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FILE 'HOME' ENTERED AT 07:03:00 ON 08 OCT 2001

=> file reg
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

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DICTIONARY FILE UPDATES:    7 OCT 2001  HIGHEST RN 360762-91-0

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

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  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> e reboxetine/cn
E1            1     REBONEX I/CN
E2            1     REBOUL COCKTAIL/CN
E3            1 --> REBOXETINE/CN
E4            1     REBOXETINE MESYLATE/CN
E5            1     REBRAMIN/CN
E6            1     REBULAC/CN
E7            1     REBULITE/CN
E8            1     REBULITE (SB5AS8TL5S22)/CN
E9            1     REBUSO/CN
E10           1     REC 0/0232/CN
E11           1     REC 0/0241/CN
E12           1     REC 0/0243/CN

=> s e3-e4
              1 REBOXETINE/CN
              1 "REBOXETINE MESYLATE"/CN
L1            2 (REBOXETINE/CN OR "REBOXETINE MESYLATE"/CN)

=> d

L1   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   98769-84-7  REGISTRY
CN   Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)-rel-,
     methanesulfonate (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, (R*,R*)-(.+-.)-,
     methanesulfonate
OTHER NAMES:
CN   Edronax
CN   FCE 20124
CN   PNU 155950E
CN   Reboxetine mesylate
FS   STEREOSEARCH
DR   98769-82-5, 141425-90-3
MF   C19 H23 N O3 . C H4 O3 S
```

[redacted]

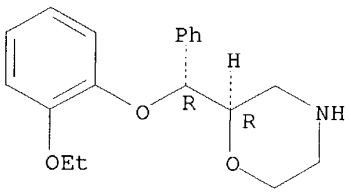
09/599,213

SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CIN, DRUGPAT, DRUGUPDATES, IPA, MRCK*, RTECS*, SYNTHLINE, TOXLINE, TOXLIT
(*File contains numerically searchable property data)

CM 1

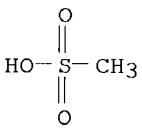
CRN 71620-89-8
CMF C19 H23 N O3

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file ca,biosis,medline,drugu,embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.41	9.56

FILE 'CA' ENTERED AT 07:03:42 ON 08 OCT 2001
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FILE 'BIOSIS' ENTERED AT 07:03:42 ON 08 OCT 2001

FILE 'MEDLINE' ENTERED AT 07:03:42 ON 08 OCT 2001

FILE 'DRUGU' ENTERED AT 07:03:42 ON 08 OCT 2001

FILE 'EMBASE' ENTERED AT 07:03:42 ON 08 OCT 2001

[redacted]

```
=> s l1 or reboxetine
L2          892 L1 OR REBOXETINE

=> s pain? or analge? or nocicep?
L3       895319 PAIN? OR ANALGE? OR NOCICEP?

=> s l2 and l3
L4           15 L2 AND L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           14 DUP REM L4 (1 DUPLICATE REMOVED)

=> d 1-14 bib,ab

L5   ANSWER 1 OF 14  CA  COPYRIGHT 2001 ACS
AN   134:285613  CA
TI   Treatment of fatigue, head injury and stroke with a selective
     noradrenaline reuptake inhibitor combined with phenylalanine or tyrosine
IN   Horrobin, David F.; Loder, Cari
PA   Laxdale Limited, UK
SO   PCT Int. Appl., 17 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 2001026623      A2    20010419      WO 2000-GB3926   20001012
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     GB 2355191          A1    20010418      GB 1999-24172    19991012
PRAI GB 1999-24172       A     19991012
AB   A method of treatment of disorders of neurol. origin and drug formulations
     for use in the method are disclosed.  These conditions comprise fatigue
     and assocd. syndromes of pain, weakness and depressed mood which
     are assocd. with chronic fatigue syndrome, brain injury and stroke,
     stress, fibromyalgia, and irritable bowel syndrome.  The treatment
     comprises administering to a patient in need thereof a selective inhibitor
     of noradrenaline reuptake combined with either phenylalanine or tyrosine
     in the same dosage form or the same pack.  The noradrenergic drug may be
     selected from lofepramine, desipramine or reboxetine.  The
     selective inhibitor may be a combined inhibitor of both noradrenaline and
     serotonin reuptake such as venlafaxine, duloxetine or milnacipran, or an
     inhibitor of both noradrenaline and dopamine reuptake such as bupropion.

L5   ANSWER 2 OF 14  CA  COPYRIGHT 2001 ACS
AN   134:173051  CA
TI   Methods and compositions for treating or preventing sleep disturbances
     using very low doses of cyclobenzaprine
IN   Iglehart, Iredell W., III
PA   Vela Pharmaceuticals, Inc., USA
SO   PCT Int. Appl., 43 pp.
```

[redacted]

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001012175	A1	20010222	WO 2000-US22082	20000811

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-148881 P 19990813

AB Methods and compns. comprising a very low dose of cyclobenzaprine or metabolite thereof are provided for preventing and treating sleep disturbances and illnesses manifested with sleep dysfunction, including fibromyalgia syndrome, chronic fatigue syndrome, sleep disorders, psychogenic **pain** disorders or chronic **pain** syndromes or symptoms thereof. Also provided are methods and compns. for treating sleep disturbances, chronic **pain** or fatigue in humans suffering from fibromyalgia syndrome, chronic fatigue syndrome, sleep disorders, psychogenic **pain** disorders, chronic **pain** syndromes using a very low dose of cyclobenzaprine.

RE.CNT 4
RE
(1) Gregorie, T; US 1339636 A 1920
(2) Khouzam; CONSULTANT 2000, V40(8), P1441
(3) Merck & Co Inc; FR 2121529 A 1972 CA
(4) Santandrea, S; JOURNAL OF INTERNATIONAL MEDICAL RESEARCH 1993, V21(2), P74 MEDLINE

L5 ANSWER 3 OF 14 CA COPYRIGHT 2001 ACS
AN 134:105849 CA
TI Highly selective norepinephrine reuptake inhibitors and methods of using the same
IN Wong, Erik H. F.; Ahmed, Saeeduddin; Marshall, Robert Clyde; McArthur, Robert; Taylor, Duncan P.; Birgerson, Lars; Cetera, Pasquale
PA Pharmacia & Upjohn Company, USA
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001001973	A2	20010111	WO 2000-US17256	20000622

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-141968 P 19990701

[redacted]

US 1999-144131 P 19990716
US 1999-158256 P 19991006
US 1999-170381 P 19991213

AB Methods and compns. for treating humans suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or a condition where inhibiting reuptake of norepinephrine is a benefit are disclosed. The compns. comprise a compd. having a high pharmacol. selectivity with respect to norepinephrine reuptake sites compared to serotonin reuptake sites. The pharmacol. selectivity of serotonin (Ki)/norepinephrine (Ki) is at least about 5000, preferably about 10,000-12,000. Examples of such compds. include **reboxetine** in an amt. of 6-10 mg/day, and more preferably optically pure (S,S) enantiomer substantially free of (R,R) **reboxetine**. The methods generally include administration of a therapeutic amt. of such compns. Prepn. of a medicament from the compn., and uses of the compn. in a manuf. of the medicament to treat a human suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or condition are also disclosed. For example, (S,S)-**reboxetine** was about 5-8 fold more potent than racemic **reboxetine** in respect to inhibiting the reuptake of norepinephrine in rats. The selectivity of Ki of serotonin/norepinephrine for (S,S)-**reboxetine** and racemic **reboxetine** was 12,770 and 81, resp.

L5 ANSWER 4 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001160947 EMBASE
TI Neurokinin(1) receptor antagonists as potential antidepressants.
AU Stout S.C.; Owens M.J.; Nemeroff C.B.
CS S.C. Stout, Lab. of Neuropsychopharmacology, Emory University School of Medicine, Department of Psychiatry, Atlanta, GA 30322, United States. sstout@learnlink.emory.edu
SO Annual Review of Pharmacology and Toxicology, (2001) 41/- (877-906).
Refs: 176
ISSN: 0362-1642 CODEN: ARPTDI
CY United States
DT Journal; General Review
FS 030 Pharmacology
032 Psychiatry
037 Drug Literature Index
LA English
SL English
AB Selective, nonpeptide antagonists for tachykinin receptors first became available ten years ago. Of the three known tachykinin receptors, drug development has focused most intensively on the substance P-preferring receptor, neurokinin(1) (NK(1)). Although originally studied as potential **analgesic** compounds, recent evidence suggests that NK(1) receptor antagonists may possess antidepressant and anxiolytic properties. If confirmed by further controlled clinical studies, this will represent a mechanism of action distinct from all existing antidepressant agents. As reviewed in this chapter, the existing preclinical and clinical literature is suggestive of, but not conclusive, concerning a role of substance P and NK(1) receptors in the pathophysiology of depression and/or anxiety disorders. The ongoing clinical trials with NK(1) receptor antagonists have served as an impetus for much needed, basic research in this field.

L5 ANSWER 5 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001163654 EMBASE
TI Depression and dysthymia.
AU Moore J.D.; Bona J.R.
CS Dr. J.D. Moore, 1365 Clifton Road Northeast, Atlanta, GA 30322, United States

09/599,213

SO Medical Clinics of North America, (2001) 85/3 (631-644).
Refs: 58
ISSN: 0025-7125 CODEN: MCNAA
CY United States
DT Journal; General Review
FS 006 Internal Medicine
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The advances made in the 1980s and 1990s have yielded many advances in the diagnosis and treatment of depression and dysthymia. Skill of the clinician is important in sorting out the diagnosis, taking care to consider the various medical conditions that can cause depression or disguise themselves as depression. Depressive disorders are highly treatable conditions. Clinicians must overcome the stigma associated with these disorders to alleviate the **pain** and suffering of those afflicted. The advances in treatment have been enormous and continue to grow. The keys to these treatments lie in continuing to acquire the knowledge to unlock all of the causes of depression. An appendix follows listing medications commonly used in the treatment of depression or for other conditions in patients under treatment for depression.

L5 ANSWER 6 OF 14 CA COPYRIGHT 2001 ACS DUPLICATE 1
AN 133:308182 CA
TI Loss of signaling through the G protein, Gz, results in abnormal platelet activation and altered responses to psychoactive drugs
AU Yang, Jing; Wu, Jie; Kowalska, M. Anna; Dalvi, Ashutosh; Prevost, Nicolas; O'Brien, Peter J.; Manning, David; Poncz, Mortimer; Lucki, Irwin; Blendy, Julie A.; Brass, Lawrence F.
CS Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA
SO Proc. Natl. Acad. Sci. U. S. A. (2000), 97(18), 9984-9989
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Heterotrimeric G proteins mediate the earliest step in cell responses to external events by linking cell surface receptors to intracellular signaling pathways. Gz is a member of the Gi family of G proteins that is prominently expressed in platelets and brain. Here, the authors show that deletion of the .alpha. subunit of Gz in mice: (i) impairs platelet aggregation by preventing the inhibition of cAMP formation normally seen at physiol. concns. of epinephrine, and (ii) causes the mice to be more resistant to fatal thromboembolism. Loss of Gz.alpha. also results in greatly exaggerated responses to cocaine, reduces the **analgesic** effects of morphine, and abolishes the effects of widely used anti-depressant drugs that act as catecholamine reuptake inhibitors. These changes occur despite the presence of other Gi.alpha. family members in the same cells and are not accompanied by detectable compensatory changes in the level of expression of other G protein subunits. Therefore, these results provide insights into receptor selectivity among G proteins and a model for understanding platelet function and the effects of psychoactive drugs.
RE.CNT 38
RE
(1) Aktories, K; Naunyn-Schmiedebergs Arch Pharmacol 1983, V324, P196 CA
(5) Casey, P; J Biol Chem 1990, V265, P2383 CA
(6) Chan, J; J Neurochem 1995, V65, P2682 CA

(7) DiMinno, G; J Pharmacol Exp Ther 1983, V225, P57 CA
(8) Drew, K; Psychopharmacology 1990, V101, P465 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09883 DRUGU P
TI **Analgesic** efficacy of **reboxetine.**
AU Schueler P; Schaffler K; Seibel K
CS Pharmacia+Upjohn; Human-Pharmacodynamic-Res.
LO Erlangen; Munich, Ger.
SO Nervenarzt (71, Suppl. 1, S132, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Pharmacia + Upjohn, Erlangen, Germany.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AB 5 Days of **reboxetine** displayed better **analgesic** effects than placebo in a randomized, double-blind, placebo-controlled, crossover study in 24 subjects in which algesia on normal and capsaicin-irritated skin was assessed objectively by laser-SEP in the vertex EEG and also on a subjective scale . Since **reboxetine** reduced the N1 and P2-components of the SEP, its **analgesic** action is assumed to have central and peripheral (probably spinal) components. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L5 ANSWER 8 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09892 DRUGU T
TI Activity of reboxetin, a selective noradrenaline-reuptake inhibitor, in patients with **pain.**
AU Harbich T; Baumann A; Niklewski G
LO Nurnberg, Ger.
SO Nervenarzt (71, Suppl. 1, S135, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Klinik fur Psychiatrie und Psychotherapie, Klinikum Nurnberg, Prof.-Ernst-Nathan-Str. 1, 90419, Nurnberg, Germany.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AB Treatment with **reboxetine** relieved or decreased **pain** in a study in 5 patients with chronic **pain** syndrome. 1 Patient had been unsuccessfully treated with opiates, NSAID and antidepressives before complete relief of **pain** by reboxetin. There were no cardiovascular side-effects and reboxetin was well tolerated. The mechanism of action of reboxetin is discussed. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L5 ANSWER 9 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09885 DRUGU T
TI Efficacy of the selective NARI **reboxetine** in **pain** patients.
AU Harbich T; Baumann A; Niklewski G
LO Nuremberg, Ger.
SO Nervenarzt (71, Suppl. 1, S133, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Klinik fuer Psychiatrie und Psychotherapie, Klinikum Nuremberg, Germany.
LA German

DT Journal
FA AB; LA; CT
FS Literature
AB When **reboxetine** was given to 5 patients with peripheral neuropathy and 1 with severe spinal myelopathy, there was a decrease in **pain** scores recorded on standardized, subjective **pain** scales. In one case, the **pain** caused by a severe spinal myelopathy had not been relieved by earlier opioids, NSAIDs, antidepressants or antiepileptics, but almost complete freedom from **pain** was achieved with **reboxetine**. These results suggest that both peripheral and central mechanisms are involved in the **analgesic** action of **reboxetine** and that alpha2-adrenoceptors may play a significant role. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L5 ANSWER 10 OF 14 MEDLINE
AN 1999129494 MEDLINE
DN 99129494 PubMed ID: 9932714
TI Activity and onset of action of **reboxetine** and effect of combination with sertraline in an animal model of depression.
AU Harkin A; Kelly J P; McNamara M; Connor T J; Dredge K; Redmond A; Leonard B E
CS Department of Pharmacology, National University of Ireland, Galway.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Jan 8) 364 (2-3) 123-32. Journal code: EN6; 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990402
Last Updated on STN: 20000303
Entered Medline: 19990324
AB The limitations of antidepressant drugs to treat depression has warranted ongoing research to identify pharmacological agents and strategies which offer a faster onset of action and greater therapeutic efficacy. Noradrenaline and serotonin are widely reported to be involved in the mechanism of action of antidepressants and the recent development of selective reuptake inhibitors of these transmitters has provided the opportunity to determine the effects of targeting these transmitter systems, alone and in combination, in an antidepressant response. The present study investigated the effects of **reboxetine**, a new antidepressant that selectively inhibits noradrenaline reuptake, sertraline, a selective serotonin reuptake inhibitor and a combination treatment composed of the two drugs in the olfactory bulbectomized (OB) rat model of depression. Sub-acute (2 days) administration of **reboxetine** (2.5, 5, and 10 mg/kg, i.p.) to sham-operated and OB rats reduced the immobility time in the forced swim test. Repeated (14 days) **reboxetine** (10 mg/kg) treatment attenuated the OB-related behavioural hyperactivity in the 'open-field' test. Examination of the onset of the antidepressant effect in the 'open-field' test demonstrated that **reboxetine** (10 mg/kg), sertraline (5 mg/kg) and the combination reduced the behavioural hyperactivity after 14 days but not before this following 3, 7 or 10 days of treatment. Reduced 5-hydroxyindoleacetic acid (5-HIAA) concentrations in amygdaloid cortex of both sham and OB rats following sertraline and combination treatments are likely to be related to acute pharmacological effects on the reuptake of 5-hydroxytryptamine (5-HT). Attenuation of the hypothermia induced by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.05 mg/kg s.c.) and

clonidine (0.1 mg/kg s.c.) occurred in the **reboxetine** and sertraline combination treated groups following both 7 and 14 days administration indicating changes to 5-HT1A receptor and alpha2-adrenoceptor sensitivity. The results indicate that changes to 8-OH-DPAT and clonidine-induced responses occur quicker with the combination treatment than with either **reboxetine** or sertraline treatments alone.

L5 ANSWER 11 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-36114 DRUGU P S
TI **Reboxetine**, a selective noradrenaline reuptake inhibitor, is non-sedative and does not impair psychomotor performance in healthy subjects.
AU Herrmann W M; Fuder H
CS Univ.Berlin-Free
LO Berlin, Ger.
SO Hum.Psychopharmacol. (13, No. 6, 425-33, 1998) 2 Fig. 2 Tab. 25 Ref.
CODEN: HUPSEC ISSN: 0885-6222
AV Klinikum Westend, Spandauer Damm 130, 14050 Berlin, Germany.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB A double-blind, randomized, 4-way crossover study was performed to assess the CNS effects of **reboxetine** (RB) compared to imipramine (IM) or placebo in 18 healthy volunteers. RB unlike IM had no sedative effects of electroencephalography or on any behavioral variable indicative of a decline in vigilance. Side-effects of RB administration included asthenia, dizziness, weakness, palpitations, inner unrest, dry mouth, impaired co-ordination, poor concentration, sensation of coldness/heat, disturbed vision, tingling sensation, cardiac arrhythmia, headache, nausea/vomiting and retrosternal **pain**.

L5 ANSWER 12 OF 14 MEDLINE
AN 1999033936 MEDLINE
DN 99033936 PubMed ID: 9818627
TI The measurement of retardation in depression.
AU Dantchev N; Widlocher D J
CS Groupe Hospitalier de la Salpetriere, Paris, France.
SO JOURNAL OF CLINICAL PSYCHIATRY, (1998) 59 Suppl 14 19-25.
Journal code: HIC; 7801243. ISSN: 0160-6689.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981202
AB The description of clinical features helps to distinguish between depressive illness and nondepressive psychic **pain** and enables the clinician to decide whether prescription of an antidepressant is beneficial. Psychomotor retardation is probably a central feature of depression, and this review discusses the methods available for measuring it. The Salpetriere Retardation Rating Scale (SRRS) specifically measures psychomotor retardation; the scale and applications are described. Means of measuring motor and speech activity and an experimental approach for understanding the process underlying psychomotor retardation are reviewed. Comparison of the SRRS and other rating scale scores demonstrates that retardation is related to depression severity and therapeutic change and

is a good criterion for prediction of therapeutic effect. The SRRS has been used to show that selective antidepressants target specific clinical dimensions of depression depending on the patient subgroup treated. Measures of motor and speech activity are sensitive to therapeutic response. Choice Reaction Time and Simple Reaction Time tasks are particularly suited for examining psychomotor retardation because they test the decision process while avoiding motivation and attention interference. Psychomotor retardation is a constant and probably central feature of depression. Means available for measuring it can be used to assess the effects of antidepressants on specific clinical dimensions.

L5 ANSWER 13 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998136598 EMBASE
TI The year's new drugs.
AU Graul A.I.
SO Drug News and Perspectives, (1998) 11/1 (15-32).
ISSN: 0214-0934 CODEN: DNPEED
CY Spain
DT Journal; General Review
FS 006 Internal Medicine
037 Drug Literature Index
LA English

L5 ANSWER 14 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999012138 EMBASE
TI [New drugs in 1998].
NEUE ARZNEIMITTEL 1998.
AU Hellwig B.
SO Deutsche Apotheker Zeitung, (17 Dec 1998) 138/51-52 SUPPL. (11-27).
ISSN: 0011-9857 CODEN: DAZEA2
CY Germany
DT Journal; General Review
FS 030 Pharmacology
037 Drug Literature Index
LA German

```
=> (noradrenaline or norepinephrine)(3a)(uptake or reuptake or
re-uptake)(5a)(inhibit? or antagoni? or block?)
(NORADRENALINE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s (noradrenaline or norepinephrine)(3a)(uptake or reuptake or
re-uptake)(5a)(inhibit? or antagoni? or block?)
   3 FILES SEARCHED...
L6        8202 (NORADRENALINE OR NOREPINEPHRINE)(3A)(UPTAKE OR REUPTAKE OR
               RE-UPTAKE)(5A)(INHIBIT? OR ANTAGONI? OR BLOCK?)

=> s l6 and l3
L7         465 L6 AND L3

=> s l6(l)l3
L8         395 L6(L) L3

=> s l6(20a)l3
L9         207 L6(20A) L3

=> dup rem l9
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PROCESSING COMPLETED FOR L9
L10 98 DUP REM L9 (109 DUPLICATES REMOVED)

=> s l10 not py>1999
L11 78 L10 NOT PY>1999

=> d 1-78 bib,ab

L11 ANSWER 1 OF 78 CA COPYRIGHT 2001 ACS
AN 132:231796 CA
TI Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity
AU Atkinson, J. H.; Slater, M. A.; Wahlgren, D. R.; Williams, R. A.; Zisook, S.; Pruitt, S. D.; Epping-Jordan, J. E.; Patterson, T. L.; Grant, I.; Abramson, I.; Garfin, S. R.
CS School of Medicine, Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
SO Pain (1999), 83(2), 137-145
CODEN: PAINDB; ISSN: 0304-3959
PB Elsevier Science B.V.
DT Journal
LA English
AB To understand the relative efficacy of noradrenergic and serotonergic antidepressants as analgesics in chronic back **pain** without depression, the authors conducted a randomized, double-blind, placebo-control head-to-head comparison of maprotiline (a **norepinephrine reuptake blocker**) and paroxetine (a serotonin reuptake blocker) in 103 patients with chronic low back **pain**. Of these 74 completed the trial; of the 29 who did not complete, 19 were withdrawn because of adverse effects. The intervention consisted of an 8-wk course of maprotiline (.ltoreq.150 mg daily) or paroxetine (.ltoreq.30 mg daily) or an active placebo, diphenhydramine hydrochloride (.ltoreq.37.5 mg daily). Patients were excluded for current major depression. Redn. in pain intensity (Descriptor Differential Scale scores) was significantly greater for study completers randomized to maprotiline compared to placebo, and to paroxetine, with a redn. of pain by 45% compared to 27% on placebo and 26% on paroxetine. These results suggest that at std. dosages noradrenergic agents may provide more effective analgesia in back pain than do selective serotonergic reuptake inhibitors.
RE.CNT 50
RE
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(2) Atkinson, J; Pain 1991, V45, P111 MEDLINE
(3) Atkinson, J; Pain 1998, V76, P287 CA
(6) Broadhead, W; J Fam Pract 1991, V33, P24 MEDLINE
(50) Yaksh, T; Prog Brain Res 1988, V77, P371 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 78 CA COPYRIGHT 2001 ACS
AN 132:132211 CA
TI Analgesic effect of intrathecal desipramine on carrageenan-induced thermal hyperalgesia in the rat
AU Kawamata, T.; Omote, K.; Kawamata, M.; Namiki, A.
CS Department of Anaesthesiology, Sapporo Medical University School of Medicine, Sapporo, 060, Japan
SO Br. J. Anaesth. (1999), 83(3), 449-452
CODEN: BJANAD; ISSN: 0007-0912
PB Oxford University Press
DT Journal

LA English
AB We examd. if intrathecal desipramine, a selective norepinephrine reuptake inhibitor, would modulate peripheral inflammation-induced hyperalgesia. Rats were chronically implanted with a lumbar intrathecal catheter and paw withdrawal latency (PWL) to noxious heat stimuli was assessed. Unilateral hindpaw inflammation was induced by intraplantar carrageenan injection. Carrageenan injection significantly ($P<0.05$) reduced PWL of the injected paw (from mean 11.4 (SEM 0.6) s to 3.5 (0.2) s, 3 h after carrageenan), but not of the contralateral side (from 11.6 (0.2) s to 11.2 (0.5) s). Intrathecal desipramine 10, 30, 60 and 100 .mu.g, which did not produce analgesic effects in untreated rats, dose-dependently reversed the shortened PWL on the ipsilateral side (3.3 (0.2), 5.3 (0.4), 6.2 (0.3) and 9.6 (0.2) s, resp.) without affecting the contralateral side. Pretreatment with intrathecal yohimbine 10 .mu.g did not antagonize the anti-hyperalgesic effects of desipramine (from 9.6 (0.2) to 9.8 (0.3) s). Our results suggest that the mechanism underlying the **analgesic** effect of desipramine on inflammation-induced hyperalgesia is unlikely to be **inhibition** of **norepinephrine reuptake** within the spinal cord.
RE.CNT 20
RE
(1) Eisenach, J; Anesthesiology 1995, V83, P1046 CA
(3) Hwang, A; Pain 1987, V28, P343 CA
(4) Kawamata, T; Anesthesiology 1997, V87, P436 CA
(10) Penning, J; Anesthesiology 1992, V77, P1186 CA
(11) Ren, K; Eur J Pharmacol 1992, V219, P235 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 78 CA COPYRIGHT 2001 ACS
AN 132:132183 CA
TI Participation of opioid mechanism in the antinociceptive effects induced by oxaprotiline enantiomers in mice
AU Wesolowska, Anna; Borycz, Jolanta
CS Department of New Drug Research, Institute of Pharmacology, Polish Academy of Sciences, Krakow, PL 31-343, Pol.
SO Pol. J. Pharmacol. (1999), 51(4), 367-371
CODEN: PJPAE3; ISSN: 1230-6002
PB Polish Academy of Sciences, Institute of Pharmacology
DT Journal
LA English
AB The purpose of the present study was to assess the activity of (+)-oxaprotiline [(+)-OXA] (a **noradrenaline uptake inhibitor**) and (-)-oxaprotiline [(-)-OXA] (with unknown mechanism of action) in two exptl. models of **pain** in mice, a hot plate test and a writhing syndrome induced by phenylbenzoquinone (PHBQ), and to det. whether the opioidergic system may be engaged in their antinociceptive effects. Morphine was used as a ref. drug. Administration of (+)-OXA (0.31-5 mg/kg) and (-)-OXA (20 mg/kg) produced a statistically significant elevation of the nociceptive threshold, measured by the increased latencies in the hot plate test. Moreover, (+)-OXA (0.62-5 mg/kg) and (-)-enantiomer (5-20 mg/kg) decreased the no. of writhing episodes induced by PHBQ in mice, (+)-enantiomer being more effective than (-)-OXA in either test. In the hot plate test, the analgesic effect induced by (+)-OXA (0.31 mg/kg) or (-)-OXA (20 mg/kg) was abolished by naloxone (2 mg/kg), an opioid receptor antagonist. In the writhing test, naloxone (2 mg/kg) partially, but not significantly, reduced the antinociceptive responses induced by (+)-OXA (0.62 mg/kg) or (-)-OXA (5 mg/kg). The obtained results show that both OXA enantiomers produce antinociception in mice which can be, at least partially, connected with opioid system.

09/599,213

RE.CNT 22
RE
(5) Delini-Stula, A; Typical and Atypical Antidepressants: Molecular Mechanisms 1982, P265 CA
(6) Gray, A; Brit J Pharmacol 1998, V124, P669 CA
(7) Hendershot, L; J Pharmacol Exp Ther 1959, V125, P237 CA
(8) Isenberg, K; Eur J Pharmacol 1984, V103, P57 CA
(10) Maj, J; J Neural Transm -Gen Sect 1990, V80, P129 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 78 CA COPYRIGHT 2001 ACS
AN 132:102336 CA
TI The role of tramadol in acute pain management
AU Budd, Keith
CS The Mornington Clinic, Bradford, UK
SO Acute Pain (1999), 2(4), 189-196
CODEN: ACPAFS; ISSN: 1366-0071
PB Saldatore Ltd.
DT Journal; General Review
LA English
AB A review with 81 refs. Tramadol hydrochloride is an opioid which has the addnl. property of **inhibiting** intersynaptic **re-uptake** of **noradrenaline** and serotonin, thus giving it a dual mode of **analgesic** action. This gives tramadol a unique place in the pain relieving armamentarium in that not only does it provide analgesia over a wide range of pathologies, but it also has significant advantages over other opioids. These include its lack of significant respiratory depressant effects, unlikely development of tolerance and dependence, and a low adverse event profile. Tramadol is esp. suited to the treatment of acute pain with a no. of formulations available and specific aspects that make it both effective and safe in problematic areas such as pediatric and cardiac surgery. Analgesia is dose-dependent, and in the awake patient, titrn. to optimal effect is recommended practice. Adverse events can be readily prevented or treated with appropriate therapy and patient compliance appears to be good. As with any agent, there are aspects about the use of tramadol that need care and attention; slow i.v. injection will reduce the incidence of nausea, and administration at the commencement of anesthesia or before wound closure will ensure that the patient awakes in comfort and with minimal occurrence of adverse events. Tramadol has proved to be a valuable addn. to the range of effective analgesic drugs, and as further aspects of its use are revealed, may well become the analgesic of choice for patients in moderate to severe pain.
RE.CNT 81
RE
(9) Bosenberg, A; Anaesthesia 1998, V53, P960 CA
(15) Bugedo, G; Br J Anaesth 1999, V83, P813 CA
(16) Cagney, B; Eur J Anaesthesiol 1999, V16, P182 CA
(17) Chen, J; Arch Intern Med 1998, V158, P2124 CA
(18) Coetzee, J; Br J Anaesth 1996, V76, P415 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 78 CA COPYRIGHT 2001 ACS
AN 131:223379 CA
TI The relationship between pupil diameter and pain by the administration of morphine and antidepressant drugs in mice
AU Onal, Aytul; Tuglular, Isik
CS Department of Pharmacology, Faculty of Medicine, Ege University, Izmir, 35100, Turk.
SO Gen. Pharmacol. (1999), 33(1), 83-89

CODEN: GEPHDP; ISSN: 0306-3623
PB Elsevier Science Inc.
DT Journal
LA English
AB Because the pain sensation is subjective, it is difficult to evaluate the responses to analgesic drugs. Some analgesics that affect the central nervous system are known to change the pupil diam. The pupil diam. is a more objective criterion that shows the drug effect. We studied the relation between the pupil diam. and **analgesia** responses to morphine and antidepressants by using the selective .mu.-receptor agonist morphine (2 and 4 mg/kg), the **noradrenaline reuptake inhibitor** desipramine (7.5 and 10 mg/kg), the mixed serotonergic and noradrenergic uptake inhibitor and cholinergic receptor antagonist amitriptyline (2.5 and 5 mg/kg), and the selective serotonin reuptake inhibitor sertraline (2.5 and 5 mg/kg) in mice. Both monocular microscopy to assess pupil measurement and the hot-plate test to assess nociceptive thresholds were used in the same animals. We found that morphine played an important role in both mydriasis and analgesia, whereas amitriptyline and desipramine had a greater effect on pupil response than on nociception. Sertraline produced antinociception without causing a change in pupil diam. As a result, although the pupil response is an important criterion in evaluating the analgesic effect of morphine, it is not possible to put forward the same criterion for the antidepressant drugs. Because different neurotransmitters are involved in pupil and pain mechanisms of antidepressant drugs, it is difficult to evaluate the analgesic response with the pupil diam.
RE.CNT 43
RE
(2) Alhaider, A; J Pharmac Exp Ther 1993, V265, P378 CA
(3) Ali, Z; Brain Res 1994, V661, P83 CA
(7) Eddy, N; J Pharmac Exp Ther 1953, V107, P385 CA
(8) El-Fakahany, E; Br J Pharmac 1983, V78, P97 CA
(9) Fanciullacci, M; Clin Pharmac Ther 1995, V57, P349 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 78 CA COPYRIGHT 2001 ACS
AN 131:214189 CA
TI Preparation of spiroindanamines and spiroindanimides as monoamine re-uptake inhibitors
IN Efange, S. Mbua Ngale; Mash, Deborah Carmen
PA Regents of the University of Minnesota, USA
SO U.S., 18 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5948807	A	19990907	US 1997-922827	19970903

OS MARPAT 131:214189
AB Spiroindanamines and spiroindanimides (I) [wherein R1 and R2 = independently H, halo, OH, CN, (un)substituted amine, lower (cyclo)alkyl, lower aloxy, or lower alkanoyl(oxy); W = (un)substituted amino; X and Y = independently 2H, S, or O; Z = (un)substituted amino or methylene], and their pharmaceutically acceptable salts, were prepd. as inhibitors of monoamine re-uptake, and are useful for treating diseases in mammals wherein insufficient synaptic levels of monoamine are implicated. Thus, 1-cyano-1-cyanomethyl-3-phenylindane (prepn. given) was heated in a mixt. of H2SO4 and AcOH and extd. with Et acetate to form cis-phenylspiro[indan-1,3'-pyrrolidine]-2',5'-dione. The dione was treated with LiAlH4 in THF

and refluxed for 20 h to yield cis-3-phenylspiro[indan-1,3'-pyrrolidine] (II). Representative compds. of the invention were tested for binding at the cocaine (SERT-1) and paroxetine (SERT-2) binding sites on the serotonin transporter, the dopamine transporter (DAT), and the mu and kappa opioid receptors. IC50 values for affinities at monoamine transporters ranged from 0.002 to 26.70 .mu.M for SERT-1, 0.3 to >100 for SERT-2, and 0.15 to 2.9 .mu.M for DAT. IC50 values for affinities at opioid receptors ranged from 0.5 to 100 .mu.M for mu opioid, and 1 to >100 .mu.M for kappa opioid. Compds. are claimed specifically as **inhibitors** of dopamine, serotonin, and **norepinephrine re-uptake**, and for treatment of **pain**, headaches, or migraines.

RE.CNT 25
RE
(2) Abou-Gharbia, M; J of Pharma Sci 1978, V67, P953 CA
(4) Anon; CH 556835 1971 CA
(5) Anon; FR 2150797 1972 CA
(6) Anon; DE 2241027 1972 CA
(7) Anon; WO 9611934 1996 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 78 CA COPYRIGHT 2001 ACS
AN 130:218530 CA
TI Characterization of the high affinity [3H]nociceptin binding site in membrane preparations of rat heart: correlations with the non-opioid dynorphin binding site
AU Dumont, Michel; Lemaire, Simon
CS Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Can.
SO J. Mol. Cell. Cardiol. (1998), 30(12), 2751-2760
CODEN: JMCDAY; ISSN: 0022-2828
PB Academic Press
DT Journal
LA English
AB The binding parameters of [3H]nociceptin were examd. in membrane prepns. of rat heart and compared with those of [3H]dynorphin A-(1-13) ([3H]Dyn A-(1-13)). Scatchard anal. of [3H]nociceptin binding revealed the presence of two distinct sites: a high affinity (Kd: 583 nM) low capacity (Bmax: 132 pmol/mg protein) site and a low affinity (Kd: 10 316 nM) high capacity (1552 pmol/mg protein) site. Dyn A and related peptides were potent competitors of the binding to the high affinity site with the following rank order of potency: .alpha.-neo-endorphin > Dyn A-(2-13) = Dyn A-(3-13) > Dyn A-(5-13) > Dyn A-(1-13) > Dyn A > Dyn B > Dyn A-(6-10) >> Dyn A-(1-8). Nociceptin was 6.7 times less potent than Dyn A with a Ki of 4.8 .mu.M as compared with 0.72 .mu.M for Dyn A. The order of potency of the various peptides in inhibiting [3H]nociceptin binding correlated well (r = 0.93) with their ability to compete with the binding of [3H]Dyn A-(1-13). In addn., the high affinity [3H]nociceptin and non-opioid [3H]Dyn A-(1-13) sites were both sensitive to NaCl (120 mM) and the phospholipase C (PLC) inhibitors, U-73122 and neomycin (100 .mu.M). The binding activities were less affected by the weak PLC inhibitor, U-73343, and no effect was obsd. with the non-hydrolyzable GTP analogs, Gpp(NH)p and GTP-.gamma.-S. **Nociceptin** (1-50 .mu.M) was also shown to **inhibit** the **uptake** of [3H]**noradrenaline** ([3H]NA) by cardiac synaptosomal prepns. In spontaneously hypertensive rats (SHR), the potency of nociceptin in inhibiting [3H]NA uptake was increased by 1.6-fold as compared with Wistar Kyoto (WKY) control rats and such effect was accompanied by comparable increased levels of cardiac ORL1 mRNA and [3H]nociceptin high affinity sites. These changes correlated well with the previously obsd. increased levels of non-opioid cardiac

[3H]Dyn A-(1-13) sites in SHR (1.3 times as compared with WKY) and increased potency of Dyn A-(1-13) in inhibiting [3H]NA uptake by cardiac synaptosomes in SHR (2.2-fold as compared with WKY). The results demonstrate that in rat heart the characteristics of the high affinity, low capacity [3H]nociceptin binding site are similar to those of the non-opioid Dyn binding site. The stimulation of this site by nociceptin, Dyn A or related peptides is more likely to produce a modulation of PLC activity and [3H]NA uptake and may participate to the pathophysiol. of hypertension. (c) 1998 Academic Press.

RE.CNT 44
RE
(1) Adapa, I; Neuropeptides 1997, V31, P403 CA
(2) Aloyo, V; Life Sci 1991, V48, P1317 CA
(4) Ardati, A; Mol Pharmacol 1997, V51, P816 CA
(5) Brodde, O; Cardiovasc Res 1995, V30, P570 CA
(6) Bunzow, J; FEBS Lett 1994, V347, P284 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 78 CA COPYRIGHT 2001 ACS
AN 129:310904 CA
TI Composition for treating pain
IN Shannon, Harlan Edgar; Whitesitt, Celia Ann
PA Eli Lilly and Co., USA
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9846601	A1	19981022	WO 1998-US7501	19980410
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9872478	A1	19981111	AU 1998-72478	19980410
PRAI	US 1997-43575		19970411		
	WO 1998-US7501		19980410		

AB Quinuclidine deriv. I and its salts and solvates, combined with a synergistic analgesic such as a NSAID, opioid, or .alpha.-adrenergic agonist, provides a novel option for treatment of pain with an acceptable profile of side effects. Types of pain treatable with this combination include esp. chronic pain such as neuropathic pain, postoperative pain, chronic lower back pain, cluster headaches, dental pain, and pain resulting from burns.

L11 ANSWER 9 OF 78 CA COPYRIGHT 2001 ACS
AN 129:211556 CA
TI Tramadol reduces the sweating, vasoconstriction, and shivering thresholds
AU De Witte, Jan L.; Kim, Jin-Soo; Sessler, Daniel I.; Bastanmehr, Hiva; Bjorksten, Andrew R.
CS Department of Anesthesia, University of California-San Francisco, San Francisco, CA, 94143-0648, USA
SO Anesth. Analg. (Baltimore) (1998), 87(1), 173-179
CODEN: AACRAT; ISSN: 0003-2999
PB Williams & Wilkins

[redacted]

09/599,213

DT Journal
LA English
AB The **analgesic** tramadol **inhibits** the neuronal **reuptake** of **norepinephrine** and 5-hydroxytryptamine, facilitates 5-hydroxytryptamine release, and activates .mu.-opioid receptors. Each of these actions is likely to influence thermoregulatory control. The authors therefore tested the hypothesis that tramadol inhibits thermoregulatory control. Eight volunteers were evaluated on four study days, on which they received no drugs, tramadol 125 mg, tramadol 250 mg, and tramadol 250 mg with naloxone, resp. Skin and core temps. were gradually increased until sweating was obsd. and then decreased until vasoconstriction and shivering were detected. The core temp. triggering each response defined its threshold. Tramadol decreased the sweating threshold by -1.03 .+-. 0.67.degree.C .mu.g-1.mL (r2 = 0.90 .+-. 0.12). Tramadol also decreased the vasoconstriction threshold by -3.0 .+-. 4.0.degree.C .mu.g-1.mL (r2 = 0.94 .+-. 0.98) and the shivering threshold by -4.2 .+-. 4.0.degree.C .mu.g-1.mL (r2 = 0.98 .+-. 0.98). The sweating to vasoconstriction interthreshold range nearly doubled from 0.3 .+-. 0.4.degree.C to 0.7 .+-. 0.6.degree.C during the administration of large-dose tramadol (P = 0.04). The addn. of naloxone only partially reversed the thermoregulatory effects of tramadol. The thermoregulatory effects of tramadol thus most resemble those of midazolam, another drug that slightly decreases the thresholds triggering all three major autonomic thermoregulatory defenses. In this respect, both drugs reduce the "setpoint" rather than produce a generalized impairment of thermoregulatory control. Nonetheless, tramadol nearly doubled the interthreshold range at a concn. near 200 ng/mL. This indicates that tramadol slightly decreases the precision of thermoregulatory control in addn. to reducing the setpoint. The authors evaluated the effects of the analgesic tramadol on the three major thermoregulatory responses: sweating, vasoconstriction, and shivering. Tramadol had only slight thermoregulatory effects. Its use is thus unlikely to provoke hypothermia or to facilitate fever.

L11 ANSWER 10 OF 78 CA COPYRIGHT 2001 ACS
AN 129:62745 CA
TI Inhibition of the nociceptive C reflex by desipramine: effect of noradrenergic denervation at the spinal level
AU Hernandez, Alejandro; Laurido, Claudio; Mondaca, Mauricio; Soto-Moyano, Ruben
CS Lab. Neurobiologia, Dep. Ciencias Biologicas, Facultad Quimica Biologia, Univ. Santiago Chile, Santiago, Chile
SO Contrib. Cient. Tecnol. (1997), 25(115), 33-40
CODEN: CCTEDC; ISSN: 0716-0127
PB Universidad de Santiago de Chile, Dep. de Investigaciones Cientificas y Tecnologicas
DT Journal
LA Spanish
AB The effects of desipramine, a tricyclic antidepressant that selectively **inhibits noradrenaline uptake**, on the **nociceptive** C-reflex were studied in rats with neurotoxic lesions of the bulbospinal noradrenergic pathways. The neurotoxic lesions were produced by intrathecal injection of 6-hydroxydopamine 2 wk prior to the expt., and later confirmed by measuring the tritiated noradrenaline uptake in spinal cord slices. The C-reflex was evoked by elec. stimulation of toes 4 and 5 and recorded as an electromyog. activity from the ipsilateral biceps femoris. Desipramine (5, 10, 20 mg/kg i.p.) induced a dose-dependent inhibition of the C-reflex responses in normal control rats, while in rats with the noradrenergic denervation the drug effects were much lower. Thus, desipramine action requires intact bulbo-spinal

noradrenergic pathways to produce analgesia. This also suggests a spinal site of action for tricyclic antidepressants with a noradrenergic profile.

L11 ANSWER 11 OF 78 CA COPYRIGHT 2001 ACS
AN 127:229117 CA
TI Nonsteroidal anti-inflammatory drugs, traditional opioids, and tramadol: contrasting therapies for the treatment of chronic pain
AU Aronson, Mark D.
CS Division of General Medicine and Primary Care, Beth Israel Hospital, Boston, MA, USA
SO Clin. Ther. (1997), 19(3), 420-432
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica
DT Journal; General Review
LA English
AB A review with 38 refs. The treatment of chronic pain is an important function of physicians. In the United States, available drug treatments for chronic pain currently include simple analgesics such as acetaminophen, salicylates and other nonsteroidal anti-inflammatory drugs, traditional opioid drugs, and adjuvant agents (eg, antidepressants, anticonvulsants). Typically, the choice of a drug is made by balancing the indications for treatment, the clin. efficacy of the drug, and its toxicity. An understanding of the mechanism of action of these drugs helps to establish their role in therapy. Tramadol is an effective **analgesic** that works through a combined mechanism of weak mu receptor binding and the **inhibition** of serotonin and **norepinephrine reuptake**. Tramadol has a favorable adverse-effect profile and therefore is likely to have an important role in the management of chronic pain syndromes.

L11 ANSWER 12 OF 78 CA COPYRIGHT 2001 ACS
AN 124:221657 CA
TI Intrathecal Tyr-W-MIF-1 produces potent, naloxone-reversible analgesia modulated by .alpha.2-adrenoceptors
AU Gergen, Kerra A.; Zadina, James E.; Kastin, Abba J.; Paul, Dennis
CS VA Medical Center and Tulane University School of Medicine, New Orleans, LA, 70146, USA
SO Eur. J. Pharmacol. (1996), 298(3), 235-9
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Spinal administration of morphine or [D-Ala2,MePhe4,Gly(ol)5]enkephalin (DAMGO) produces potent, naloxone-reversible analgesia that is modulated by .alpha.2-adrenoceptors. Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH2) is a naturally occurring, amidated tetrapeptide that is structurally related to the MSH release inhibiting factor-1 (MIF-1) family of endogenous peptides. Tyr-W-MIF-1 displays high selectivity for the .mu.-opioid receptor. We investigated the effect of spinal administration of Tyr-W-MIF-1 on analgesia using the mouse tail-flick assay. Intrathecal (i.t.) administration of Tyr-W-MIF-1 produced a dose-dependent analgesic response, with an ED50 of 0.41 .mu.g, that was reversed by naloxone. Pretreatment with the .mu.-opioid receptor-selective antagonist .beta.-funaltrexamine blocked the effect of i.t. Tyr-W-MIF-1. However, pretreatment with the .mu.1-opioid receptor-selective antagonist naloxonazine did not antagonize the analgesia, indicating the effect was mediated through spinal .mu.2-opioid receptors. Pretreatment with desipramine, an **inhibitor** of **norepinephrine reuptake**, potentiated the **analgesic** effect of i.t. Tyr-W-MIF-1, producing a 3.1-fold leftward shift in the dose-response curve. Spinal administration of yohimbine, an .alpha.2-adrenoceptor-

selective antagonist, significantly attenuated the analgesic effect of Tyr-W-MIF-1. Thus, the potent analgesic effect of i.t. Tyr-W-MIF-1 is mediated through spinal .mu.2-receptors, and is modulated by norepinephrine and .alpha.2-adrenoceptors.

L11 ANSWER 13 OF 78 CA COPYRIGHT 2001 ACS
AN 123:246079 CA
TI Serotonin and **norepinephrine uptake inhibiting** activity of centrally acting **analgesics**: structural determinants and role in antinociception
AU Codd, Ellen E.; Shank, Richard P.; Schupsky, James J.; Raffa, Robert B.
CS Drug Discovery Res., R. W. Johnson Pharm. Res. Inst., Spring House, PA, USA
SO J. Pharmacol. Exp. Ther. (1995), 274(3), 1263-70
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB Although it is well established that the **analgesic** effects of morphine are mediated by opioid receptors, previous studies have shown that some opioids addnl. **inhibit** the **uptake** of serotonin and **norepinephrine**. The present investigation of a diverse group of opioids revealed that structurally identifiable subgroups inhibited the neuronal reuptake of these monoamines. Phenanthrene opioids with an oxygen bridge between C4 and C5, such as morphine and naloxone (group I), did not block norepinephrine or serotonin uptake, whereas phenanthrene opioids without the oxygen bridge and the C6-OH moiety, such as levorphanol and levomethorphan (group II), did inhibit uptake, as did nonphenanthrene opioids, such as d-propoxyphene and methadone (group III). Affinity at the mu opioid receptor correlated with antinociceptive potency (r = 0.87). Although the antinociceptive activity of the "active enantiomers" of group II and III compds. also correlated with their affinity at the mu opioid receptor (r = 0.85), addnl. consideration of serotonin uptake inhibiting activity (but not of norepinephrine uptake inhibiting activity) significantly improved the correlation between antinociceptive potency and the in vitro activity of these compds. (r = 0.915). Addnl., for group II and III (but not group I) compds., smaller differences between enantiomers in antinociceptive potency than in mu receptor affinity were noted, presumably because of the contribution of uptake inhibition to the antinociceptive activity of group II and III compds. Evidence also is provided suggesting a broader role for the combination of mu opioid affinity and 5-hydroxytryptamine uptake inhibition in the activity of other antinociceptive agents.

L11 ANSWER 14 OF 78 CA COPYRIGHT 2001 ACS
AN 121:73757 CA
TI **Inhibition** of spinal **noradrenaline uptake** in rats by the centrally acting **analgesic** tramadol
AU Reimann, Wolfgang; Hennies, Hagen-Heinrich
CS Department of Pharmacology, Gruenenthal GmbH, Aachen, 52078, Germany
SO Biochem. Pharmacol. (1994), 47(12), 2289-93
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Tramadol is a centrally acting analgesic with low affinity to opioid receptors. A further mode of action is inhibition of noradrenaline uptake as measured in std. assays. Since tramadol shows antinociception at the spinal site, it was to be tested whether uptake blockade could be verified in spinal tissue. Therefore, synaptosomes and slices had to be prepd. from the dorsal half of the spinal cord and the uptake of [3H]noradrenaline into synaptosomes to be characterized. The uptake was

linear for at least 3 min. The apparent Km was 0.16 .mu.M and Vmax was 7.9pmol/mg protein. Tramadol inhibited the uptake competitively as analyzed with Dixon plots with a Ki of 0.6 .mu.M. Uptake inhibition was affected in order of potency by (+)-oxaprotiline > nisoxetine >(-)-tramadol >(-)-oxaprotiline = tramadol > (+)-tramadol. Slices were preincubated with [3H]noradrenaline then superfused and simulated elec. Nisoxetine, tramadol and its (-)-enantiomer enhanced mainly the stimulation-evoked overflow indicating uptake inhibition without releasing effects. Expts. with inclusion of the noradrenaline uptake inhibitor desipramine provided evidence that tramadol interfered with the noradrenaline transporter. The results show that spinal synaptosomes and slices are valid prepns. to study local noradrenaline uptake and release. Tramadol enhances extraneuronal noradrenaline levels in the spinal cord by competitive interference with the noradrenaline uptake mechanism.

L11 ANSWER 15 OF 78 CA COPYRIGHT 2001 ACS
AN 120:45706 CA
TI Evaluation of nefopam as a monoamine uptake inhibitor in vivo in mice
AU Fuller, Ray W.; Snoddy, Harold D.
CS Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Neuropharmacology (1993), 32(10), 995-9
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB Nefopam antagonized 6-hydroxydopamine-induced depletion of heart norepinephrine in mice with an ED50 value of 12 mg/kg. Nefopam was ineffective in antagonizing p-chloroamphetamine-induced depletion of brain serotonin in the authors' std. assay in mice, apparently due to a short duration of action. Brain concns. of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) were decreased after a 32 mg/kg, i.p., dose of nefopam at 1 and 2 h but not at 4 h. When nefopam was injected simultaneously with p-chloroamphetamine, it prevented brain serotonin depletion initially, but by 6 h the protective effect was essentially lost, suggesting that p-chloroamphetamine persisted in mouse brain longer than did nefopam. Nefopam caused a dose-related antagonism of brain serotonin depletion at 2 h after injection of a low dose of p-chloroamphetamine hydrochloride (10 mg/kg, i.p.), with a calcd. ED50 value of 11 mg/kg. The lowering of brain 5-HIAA concn. 2 h after nefopam injection occurred after a 32 mg/kg dose but not after a 3 or 10 mg/kg dose. These data suggest that nefopam is effective as an **inhibitor** of **norepinephrine** and serotonin **uptake** at doses previously shown to be **analgesic** in mice, consistent with uptake inhibition being a postulated mechanism important in its **analgesic** effect. Nonetheless, nefopam is a relatively weak inhibitor of monoamine uptake with a short duration of action in mice.

L11 ANSWER 16 OF 78 CA COPYRIGHT 2001 ACS
AN 117:62841 CA
TI Involvement of beta-adrenoceptors in the antinociceptive effect of desipramine in mice
AU Mico, Juan Antonio; Brochet, Denis; Casas, Juan; Gibert-Rahola, Juan; Simon, Pierre
CS Dep. Neurocienc., Fac. Med., Cadiz, 11003, Spain
SO Med. Sci. Res. (1992), 20(11), 405-6
CODEN: MSCREJ; ISSN: 0269-8951
DT Journal
LA English
AB Beta-adrenoceptors are involved in depression and in the effects of antidepressants. Their stimulation induces an antidepressant activity in humans, and their blockade antagonizes the effect of antidepressants in

mice. These relationships prompted the authors to investigate the possible implication of beta-adrenoceptors in the antinociceptive action in mice of desipramine. This tricyclic antidepressant is a potent **inhibitor** of the presynaptic **uptake** of **noradrenaline**, and its **analgesic** properties have been demonstrated in exptl. **pain**. It seems likely that beta-adrenoceptors may participate in the antinociceptive effects of antidepressants, as they contribute to their antidepressant activity. However, further studies are needed to det. whether the implication of these receptors is a common feature of the antinociceptive action of various antidepressant treatments.

L11 ANSWER 17 OF 78 CA COPYRIGHT 2001 ACS
AN 117:20270 CA
TI EM 405: a new compound with analgesic and antiinflammatory properties and no gastrointestinal side-effects
AU Selve, N.; Friderichs, E.; Graudums, I.
CS Dep. Pharmacol., Gruenenthal GmbH, Aachen, W-5100, Germany
SO Agents Actions (1992), (Spec. Conf. Issue), C84-C85
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English
AB EM 405 has **analgesic** and antitussive effects, probably exerted by **noradrenaline uptake inhibition** and local anesthetic actions. It showed antiinflammatory, which may be due to antihistaminic and indirect sympathomimetic properties. As oral application of EM 405 did not induce gastrointestinal side effects a possible ulcer preventing action was investigated. EM 405 reduced gastric ulcers induced by ethanol or indomethacin with oral ED50 values of 45 and 26 mg/kg. Stress-induced ulcer was inhibited with an ED50 of 34 mg/kg. EM 405 reduced basal and stimulated gastric secretion by reducing vol. as well as H+ - and Cl--prodn. Therefore ulcer prevention by EM 405 may be explained by its inhibitory effects on gastric secretion. The results characterize EM 405 as a novel antiinflammatory compd. with ulcer-protective action.

L11 ANSWER 18 OF 78 CA COPYRIGHT 2001 ACS
AN 116:228055 CA
TI Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro
AU Driessen, B.; Reimann, W.
CS Abt. Pharmakol., Gruenenthal GmbH, Aachen, W-5100, Germany
SO Br. J. Pharmacol. (1992), 105(1), 147-51
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal
LA English
AB Tramadol is a centrally acting analgesic with low opioid receptor affinity and therefore presumably other mechanisms of analgesic action. Tramadol **inhibits noradrenaline uptake** but since 5-hydroxytryptamine (5-HT) is also involved in the modulation of **pain** perception, the authors tested the effects of tramadol on 5-HT uptake and release in vitro. Tramadol inhibited the uptake of [3H]-5-HT into purified rat frontal cortex synaptosomes with an IC50 of 3.1 .mu.M. The (+)-enantiomer was about four times more potent than the (-)-enantiomer; the main metabolite of tramadol, O-desmethyltramadol, was about ten times less potent. Rat frontal cortex slices were preincubated with [3H]-5-HT, then superfused and stimulated elec. Tramadol facilitated the basal outflow of [3H]-5-HT, at concns. greater than 1 .mu.M, while the uptake inhibitor 5-nitroquipazine enhanced both basal and stimulation-evoked overflow. The effects of the (+)-enantiomer were more

potent than either the racemate, the (-)-enantiomer or the principal metabolite. The effects of tramadol on the basal outflow of [3H]-5-HT were almost completely abolished when the superfusion medium contained a high concn. of the selective 5-HT uptake blocker, 6-nitroquipazine. The results provide evidence for an interaction of tramadol with the neuronal 5-HT transporter. An intact uptake system is necessary for the enhancement of extraneuronal 5-HT concns. by tramadol, indicating an intraneuronal site of action.

L11 ANSWER 19 OF 78 CA COPYRIGHT 2001 ACS
AN 113:184237 CA
TI The effect of nefopam and its enantiomers on the uptake of 5-hydroxytryptamine, noradrenaline and dopamine in crude rat brain synaptosomal preparations
AU Rosland, Jan Henrik; Hole, Kjell
CS Dep. Physiol., Univ. Bergen, Bergen, Norway
SO J. Pharm. Pharmacol. (1990), 42(6), 437-8
CODEN: JPPMAB; ISSN: 0022-3573
DT Journal
LA English
AB The effect of (.+-.), (+) and (-)-nefopam on the uptake of 5-hydroxytryptamine (5-HT), noradrenaline and dopamine in synaptosomal prepns. from rat forebrain, hippocampus and striatum has been investigated. All 3 forms of nefopam inhibited the amine uptake in the investigated structures, the order of potency being (+) > (.+-.) > (-). (+)-Nefopam was 7-30 times more potent than (-)-nefopam. The same order of potency has also been found for the antinociceptive effect of these three forms, however, the differences were smaller. **Inhibition** of 5-HT and **noradrenaline uptake** may not be the sole mechanism underlying the **analgesic** effect of nefopam.

L11 ANSWER 20 OF 78 CA COPYRIGHT 2001 ACS
AN 109:66756 CA
TI Potentiation of morphine analgesia by d-amphetamine is mediated by norepinephrine and not dopamine
AU Izenwasser, Sari; Kornetsky, Conan
CS Sch. Med., Boston Univ., Boston, MA, 02118, USA
SO Pain (1988), 33(3), 363-8
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB Morphine will raise the threshold for escape from aversive elec. stimulation delivered to the mesencephalic reticular formation and this effect is potentiated by d-amphetamine. The effects of amfonelic acid, an indirect dopamine agonist, and nisoxetine, a selective **norepinephrine reuptake blocker**, were detd. alone and in combination with morphine by using this supraspinal model of **analgesia** in rats. Amfonelic acid alone produced hyperalgesia and completely antagonized the analgesic effect of morphine. Nisoxetine had no effect by itself; however, it potentiated the analgesic effect of morphine when the 2 drugs were administered concomitantly. Thus, norepinephrine and not dopamine plays a predominant role in the potentiation of opiate analgesia by d-amphetamine.

L11 ANSWER 21 OF 78 CA COPYRIGHT 2001 ACS
AN 108:68748 CA
TI Effects of graded oral doses of a new 5-hydroxytryptamine/ **noradrenaline uptake inhibitor** (Ro 15-8081) in comparison with 60 mg codeine and placebo on experimentally induced **pain** and side effect profile in healthy men

09/599,213

AU Stacher, G.; Steinringer, H.; Schneider, S.; Mittelbach, G.; Gaupmann, G.; Abatzi, T. A.; Stacher-Janotta, G.
CS Dep. Psychiatry, Univ. Vienna, Vienna, A-1090, Austria
SO Br. J. Clin. Pharmacol. (1987), 24(5), 627-35
CODEN: BCPHBM; ISSN: 0306-5251
DT Journal
LA English
AB Ro 15-8081 (I) at oral doses of 10, 25, and 50 mg in healthy humans elevated the threshold and tolerance to elec. and the threshold to thermally induced cutaneous pain to about the same degree as did codeine (60 mg orally), although the onset of action for I was somewhat slower than after codeine. I had no effects on psychomotor function or subjective feelings indicative of altered central nervous system arousal, well-being, and mood. I produced an only slightly higher no. of side effects (such as abdominal discomfort, headache, and nausea) than did placebo.

L11 ANSWER 22 OF 78 CA COPYRIGHT 2001 ACS
AN 106:168492 CA
TI Stereospecific potentiation of opiate analgesia by cocaine: predominant role of noradrenaline
AU Misra, Anand L.; Pontani, Ronald B.; Vadlamani, Narasimham L.
CS Test. Res. Lab., New York State Div. Subst. Abuse Serv., Brooklyn, NY, 11217, USA
SO Pain (1987), 28(1), 129-38
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB Cocaine [50-36-2] (50 mg) pellets implanted s.c. in male Wistar rats potentiated the analgesia of morphine [57-27-2], levorphanol [77-07-6], methadone [76-99-3] and buprenorphine [52485-79-7] as measured by the tail-withdrawal test. Potentiated opiate analgesia was abolished by naloxone and further enhanced by noradrenaline [51-41-2] inhibitors, desipramine and phenoxybenzamine. Yohimbine, .alpha.-Me p-tyrosine, haloperidol, zimelidine, methysergide, p-chlorophenylalanine produced no significant effect on potentiated opiate analgesia. Pseudococaine, dextro-cocaine [478-73-9], which is several-fold less potent than cocaine as an **inhibitor** of **noradrenaline** and dopamine **reuptake** in the CNS, had no significant effect on opiate **analgesia**. Analgesia produced by low doses of baclofen, a GABA agonist, was also not potentiated by cocaine. This study suggests a predominant role for noradrenaline in the stereospecific potentiation of opiate analgesia by cocaine.

L11 ANSWER 23 OF 78 CA COPYRIGHT 2001 ACS
AN 96:155360 CA
TI The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine
AU Pekoe, Gary M.; Smith, David J.
CS Med. Cent., West Virginia Univ., Morgantown, WV, 26506, USA
SO Pain (1982), 12(1), 57-73
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB The analgesic action of both ketamine (I) [6740-88-1] and morphine (II) [57-27-2], as measured by the tail-flick test in rats, was inhibited by norepinephrine, serotonin and opiate receptor antagonists. Monoaminergic receptor inhibitors were more potent as antagonists of ketamine analgesia while the opiate receptor antagonist naloxone was more effective against morphine. The greater sensitivity of the antinociceptive effect of

ketamine to monoaminergic antagonist may reflect the importance of the **inhibition** of **norepinephrine** and serotonin **reuptake** in the **analgesic** action of the drug. Transecting the spinal cord of rats at T4-6 revealed distinct differences between the analgesic mechanisms of ketamine and morphine. The potency of ketamine was increased nearly 9-fold in spinal rats whereas that of morphine was decreased. This observation suggests that ketamine may activate both analgesic and antianalgesic systems supraspinally, and that its antinociceptive effect in intact animals is a summation of these opposing actions. Partial evidence that supraspinal noradrenergic neurons might be involved in the antianalgesic component of ketamine's action was provided by expts. demonstrating enhanced analgesia in intact animals after depletion of norepinephrine with FLA-63. In spinal animals a significant difference was also obsd. in the neuronal processes mediating the residual analgesic effects of morphine and ketamine. The analgesic effect of morphine remained primarily sensitive to naloxone but seemed to use a local serotonergic process (sensitive to the serotonergic antagonist methysergide) at higher doses of the opiate. Ketamine analgesia, on the other hand, was only inhibited by methysergide. Although it appears that morphine and ketamine may both activate spinopetal monoaminergic processes through an opiate mechanism, the 2 drugs differ significantly with regard to some of the components of their antinociceptive actions. The differences may be related to ketamine's ability to alter the metab. of monoaminergic neurotransmitters involved in pain processing.

L11 ANSWER 24 OF 78 CA COPYRIGHT 2001 ACS
AN 93:125585 CA
TI Test-specific effects of the 5-HT reuptake inhibitors alaproclate and zimelidine on pain sensitivity and morphine analgesia
AU Oegren, S. O.; Holm, A. C.
CS Res. Dev. Lab., Astra Lakemedel AB, Sodertalje, Swed.
SO J. Neural Transm. (1980), 47(4), 253-71
CODEN: JNTMAH; ISSN: 0300-9564
DT Journal
LA English
AB The effects of the specific 5-hydroxytryptamine (5-HT) uptake inhibitors alaproclate-HCl (I) [60719-83-7] and zimelidine-HCl (II) [60525-15-7] the 5-HT releasing compd. p-chloroamphetamine (PCA) and the specific **noradrenaline uptake inhibitor** desipramine or **pain** sensitivity were examd. in rats using the hot-plate and tail-flick methods. The effects of alaproclate and zimelidine on 5-HT uptake mechanisms in the hypothalamus and spinal cord were also studied. Alaproclate, zimelidine, PCA, and desipramine produced hypalgesia in the hot-plate but not in the tail-flick test. Naloxone (1 mg/kg) failed to block the hypalgesia produced by alaproclate and PCA in the hot-plate test. Zimelidine but not desipramine pretreatment blocked the analgesic action of PCA in the hot-plate test. Alaproclate significantly enhanced morphine sulfate [64-31-3] analgesia in the hot-plate test but did not affect morphine analgesia in the tail-flick test. In contrast, zimelidine tended to enhance and significantly prolonged morphine analgesia in the tail-flick test but did not affect morphine analgesia in the hot-plate test. Zimelidine inhibited 5-HT uptake with equal potency in the hypothalamus and spinal cord, whereas alaproclate produced a greater inhibition of 5-HT uptake in the hypothalamus. Thus various aspects of pain sensitivity and morphine analgesia may involve different 5-HT pathways in the brain and spinal cord. Moreover, 5-HT pathways in the forebrain may mediate analgesia of a non-opiate type.

L11 ANSWER 25 OF 78 CA COPYRIGHT 2001 ACS
AN 89:16834 CA

TI The effect of clomipramine and other amine-uptake inhibitors on morphine analgesia in laboratory animals
AU Lee, R. L.; Spencer, P. S. J.
CS Welsh Sch. Pharm., Univ. Wales Inst. Sci. Technol., Cardiff, Wales
SO Postgrad. Med. J., Suppl. (1977), 53(4), 53-61
CODEN: PMESAJ; ISSN: 0370-0593
DT Journal
LA English
AB Single dose administration of clomipramine-HCl [17321-77-6] enhanced the analgesic action of morphine-HCl (I-HCl) [52-26-6] in lab. mice and rats. By contrast, maprotiline [10262-69-8] (a tricyclic antidepressant with marked specificity for **inhibiting noradrenaline uptake**) reduced the **analgesic** effect of I. Neither amitriptyline-HCl [549-18-8] nor nortriptyline-HCl [894-71-3] (both nonspecific **inhibitors** of **noradrenaline** and 5-hydroxytryptamine **uptake**) significantly affected the level of I **analgesia**. These and other findings accord with the theory of central noradrenaline/5-hydroxytryptamine balance. Studies with chlorpromazine-HCl [69-09-0] showed marked potentiation of I analgesia. The effects of clomipramine and maprotiline on pentazocine-HCl analgesia were also studied, with results similar to those for I. Repeated-dose studies with I showed that combination with clomipramine induced more severe tolerance more rapidly, whereas maprotiline delayed and alleviated I tolerance.

L11 ANSWER 26 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:36086 BIOSIS
DN PREV200000036086
TI Effects of tramadol and its enantiomers on Concanavalin-A induced-proliferation and NK activity of mouse splenocytes: Involvement of serotonin.
AU Sacerdote, P. (1); Bianchi, M.; Gaspani, L.; Panerai, A. E.
CS (1) Department of Pharmacology, University of Milan, via Vanvitelli 32, 20129, Milano Italy
SO International Journal of Immunopharmacology, (Nov., 1999) Vol. 21, No. 11, pp. 727-734.
ISSN: 0192-0561.
DT Article
LA English
SL English
AB The centrally acting **analgesic** drug tramadol is a 1:1 racemic mixture of two enantiomers, with different pharmacological properties. The (-)-tramadol preferentially **inhibits noradrenaline uptake**, whereas the (+)-tramadol **inhibits** serotonin uptake and binds to opioid receptors. Since tramadol has been shown to stimulate some immune responses in mice, in the present work we analyzed the effects of its enantiomers on the same parameters, with the aim to better characterize the mechanisms involved in such action of tramadol. The acute administration of 20 and 40 mg/kg of racemic tramadol and of 10 and 20 mg/kg of (+)-tramadol induced a significant and comparable stimulation of Concanavalin-A (Con-A) induced proliferation and of Natural Killer (NK) activity of splenocytes. On the contrary, the (-)-tramadol was devoid of any effect. The pretreatment with the serotoninergic antagonist metergoline (3.0 mg/kg) completely blocked the effects of both tramadol and (+)-tramadol. We suggest that theenhancement of the serotoninergic tone could be at the basis of the stimulatory effects exerted by tramadol on Con-A induced lymphoproliferation and NK activity.

L11 ANSWER 27 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:460696 BIOSIS

DN PREV199900460696
TI Fatal nefopam overdose.
AU Urwin, S. C. (1); Smith, H. S.
CS (1) Peterborough District Hospital, Thorpe Road, Peterborough, PE3 6DA UK
SO British Journal of Anaesthesia, (Sept., 1999) Vol. 83, No. 3, pp. 501-502.
ISSN: 0007-0912.
DT Article
LA English
SL English
AB Nefopam is a non-opioid **analgesic** agent with a central mode of action involving activation of descending **pain**-modulating pathways and **inhibition** of synaptosomal **uptake** of hydroxytryptamine, **norepinephrine** and dopamine. Adverse effects during therapeutic use and after overdose of nefopam are known to involve the central nervous system (confusion and convulsions), the cardiovascular system (tachycardia and palpitations) and the kidneys (oliguria and renal failure). We report a death after nefopam overdose in a young woman who exhibited many of these features. It is only the second case of death after nefopam overdose in the literature.

L11 ANSWER 28 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:213502 BIOSIS
DN PREV199900213502
TI Tissue distribution of tramadol and metabolites in an overdose fatality.
AU Moore, Karla A. (1); Cina, Stephen J.; Jones, Robert; Selby, Dale M.; Levine, Barry; Smith, Michael L.
CS (1) Forensic Toxicology, AFIP, 1413 Research Boulevard, Building 102, Rockville, MD, 20850-3125 USA
SO American Journal of Forensic Medicine and Pathology, (March, 1999) Vol. 20, No. 1, pp. 98-100.
ISSN: 0195-7910.
DT Article
LA English
SL English
AB Tramadol (Ultram) is a centrally acting, synthetic **analgesic** agent. Although it has some affinity for the opiate receptors, tramadol is believed to exert its **analgesic** effect by **inhibiting** the **re-uptake** of **norepinephrine** and serotonin. There are several published cases of tramadol's involvement in drug-related deaths and impairment. Reports of deaths involving tramadol alone with associated tissue concentrations are rare. This report documents a case in which tramadol overdose was identified as the cause of death. The following tramadol concentrations were found in various tissues: blood, 20 mg/L; urine, 110.2 mg/L; liver, 68.9 mg/kg; and kidney, 37.5 mg/kg. Tissue distributions of the two primary metabolites, N-desmethyl and O-desmethyl tramadol, are also reported. In each tissue or fluid except urine, the tramadol concentration was greater than either metabolite, consistent with other reports of drug-impaired drivers and postmortem cases. The O-desmethyl metabolite concentration was greater than the N-desmethyl metabolite concentration in all tissues; this is in contrast to other postmortem reports, in which the majority of cases report concentrations of O-desmethyl as less than those of N-desmethyl. This may be useful as an indicator of time lapse between ingestion and death.

L11 ANSWER 29 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:452948 BIOSIS
DN PREV199800452948
TI Effects of mesaconitine on (3H) noradrenaline uptake and neuronal excitability in rat hippocampus.

09/599,213

AU Ameri, Angela (1); Seitz, Ulrike
CS (1) Dep. Pharm. Pharmacol. Nat. Compounds, Univ. Ulm, Helmholtzstrasse 20, D-89081 Ulm Germany
SO Experimental Brain Research, (Aug., 1998) Vol. 121, No. 4, pp. 451-456. ISSN: 0014-4819.
DT Article
LA English
AB Mesaconitine, one of the main alkaloids contained in Aconiti tubers, is a centrally acting analgesic without affinity to opioid receptors. It has been reported that the antinociception is due to an interaction with the noradrenergic system. In the present study, the effect of mesaconitine on the uptake of noradrenaline and on neuronal activity was examined in rat hippocampus. Experiments were performed as a study of (3H)noradrenaline uptake into rat hippocampal synaptosomes. Mesoconitine inhibited (3H)noradrenaline uptake in a concentration-dependent manner with a Ki of 111.95 +- 18 nM. In a further series of experiments, the effects of mesaconitine on the extracellularly recorded population spike were investigated in rat hippocampal slices. At a concentration of 10 nM, mesaconitine increased the amplitude of the postsynaptic population spike by 31.10% +- 6.7% of control and elicited one or two additional spikes. The presynaptic fiber spike and the field excitatory postsynaptic potential were not affected by this alkaloid. The enhancement of neuronal activity was abolished by 1 muM propranolol as well as by 1 muM timolol. It is concluded that mesoconitine increased the excitability in rat hippocampal pyramidal cells by an involvement of the noradrenergic system, with at least one mechanism being inhibition of noradrenaline uptake leading to an enhanced extraneuronal noradrenaline level.

L11 ANSWER 30 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:451554 BIOSIS
DN PREV199800451554
TI Antidepressant treatment of chronic tension-type headache: A comparison between fluoxetine and desipramine.
AU Walker, Zuzana (1); Walker, Rodney W. H.; Robertson, Mary M.; Stansfeld, Stephen
CS (1) Dep. Psychiatry and Behavioural Sci., Univ. Coll. London Med. Sch., Wolfson Build., Riding House St., London W1N 8AA UK
SO Headache, (July-Aug., 1998) Vol. 38, No. 7, pp. 523-528. ISSN: 0017-8748.
DT Article
LA English
AB Amitriptyline, which is a noradrenaline reuptake and 5-HT reuptake inhibitor, has an established role in the management of chronic tension-type headaches. In a single-blind study, patients with chronic tension-type headache were randomized to either fluoxetine 20 mg (a selective 5-HT reuptake inhibitor) or desipramine 75 mg (a selective **noradrenaline reuptake inhibitor**) and followed for 12 weeks to compare the effectiveness of the two drugs in improving headache, and to assess whether **pain** control is related to changes in depression. Patients were evaluated at weekly intervals on an analog pain-rating scale and at 4-weekly intervals on the Montgomery and Asberg Depression Rating Scale (MADRS), the MOS general health status questionnaire (SF36), the Hospital Anxiety and Depression Scale (HADS), and a side effects checklist. Eighteen patients were randomized to take fluoxetine and 19 to take desipramine. Of the 25 patients who completed the trial, 12 were on fluoxetine and 13 were on desipramine. There was no significant difference between the two groups at baseline nor in change of pain; reduction in use of analgesic medication; nor change in the HADS, MADRS, or SF36 scores at 12 weeks, but 72% of patients who completed the study improved, and this improvement almost exactly mirrored the

improvement on the MADRS. The results from this trial are compatible with the notion that the beneficial effect of antidepressants in chronic tension-type headache is indirect, mediated by an effect on depression, and not more, dependent on serotonin reuptake inhibition than noradrenaline reuptake inhibition.

L11 ANSWER 31 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:405688 BIOSIS
DN PREV199799711891
TI Seizure after overdose of tramadol.
AU Tobias, Joseph D.
CS Dep. Child Health, Univ. Missouri, M658 Health Sci. Cent., One Hospital Dr., Columbia, MO 65212 USA
SO Southern Medical Journal, (1997) Vol. 90, No. 8, pp. 826-827. ISSN: 0038-4348.
DT (CASE STUDY)
LA English
AB Tramadol (Ultram) is a new **analgesic** agent with a dual mechanism of action that includes weak agonistic effects at the mu-opioid receptor as well as **inhibition** of neurotransmitter (serotonin, **norepinephrine**) **re-uptake**. Although it has proven to be a safe and effective agent for the control of **pain**, adverse effects can occur with its use. I report the occurrence of seizure activity after the inadvertent administration of 4 mg/kg of tramadol to a child. Previous reports of seizure activity after tramadol administration are reviewed and the treatment of this problem is discussed.

L11 ANSWER 32 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:208759 BIOSIS
DN PREV199799507962
TI The effects of different monoaminergic antidepressants on the analgesia induced by spinal cord adrenal medullary transplants in the formalin test in rats.
AU Ortega-Alvaro, Antonio; Gibert-Rahola, Juan; Mellado-Fernandez, Manuel L.; Chover, Antonio J.; Mico, Juan A. (1)
CS (1) Dep. Neurociencias, Fac. Med., Fragela s/n, 11003 Cadiz Spain
SO Anesthesia & Analgesia, (1997) Vol. 84, No. 4, pp. 816-820. ISSN: 0003-2999.
DT Article
LA English
AB We studied the effects of chronic intraperitoneal administration of antidepressants on the antinociception induced by adrenal medullary transplants into the subarachnoid space in rats using the formalin test. Administration of drugs started 28 days after operation and the formalin test was performed on Day 56. When amitriptyline (AMT; 15 mg cntdot kg-1 cntdot day-1) was administered to sham-operated rats, it decreased the licking time and increased the transplant-induced analgesia in Phase I when administered to transplanted rats. Chronic treatment with fluvoxamine (FVX, 10 mg cntdot kg-1 cntdot day-1) had no influence on the licking response in sham rats, nor did it modify the transplant induced analgesia when administered to transplanted rats. When desipramine (DMI; 10 mg cntdot kg-1 cntdot day-1) was administered to sham rats, it significantly reduced the licking response in Phase 1, but when administered to transplanted rats it did not increase the transplant-induced analgesia. None of the drugs administered showed any effect on Phase 2 of the formalin test. These results suggest that adrenal medullary transplants into the spinal cord induce **analgesia** as determined by the formalin test. This effect is more pronounced when AMT (a nonselective **noradrenaline**-serotonin **reuptake inhibitor**) is chronically administered, but not when FVX or DMI are chronically

administered.

L11 ANSWER 33 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:516711 BIOSIS
DN PREV199598531011
TI Opposite effects of duloxetine, a serotonin (5HT) and **norepinephrine** (NE) **re-uptake inhibitor**, on **nociceptive** reflexes to the bladder and urethral sphincter.
AU Thor, K. B.; Katofiasc, M. A.
CS Eli Lilly Co., Indianapolis, IN 46285 USA
SO Society for Neuroscience Abstracts, (1995) Vol. 21, No. 1-3, pp. 1874. Meeting Info.: 25th Annual Meeting of the Society for Neuroscience San Diego, California, USA November 11-16, 1995 ISSN: 0190-5295.
DT Conference
LA English

L11 ANSWER 34 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:350826 BIOSIS
DN PREV199598365126
TI Profiles of the Antinociceptive Effect of R-84760, a Selective kappa-Opioid Receptor Agonist, in the Formalin Test in Mice.
AU Fujibayashi, Kenji; Iizuka, Yoshio
CS Biol. Res. Lab., Sankyo Co. Ltd., 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo 140 Japan
SO Japanese Journal of Pharmacology, (1995) Vol. 68, No. 1, pp. 57-63. ISSN: 0021-5198.
DT Article
LA English
AB The antinociceptive effect of a selective kappa-opioid receptor agonist R-84760, (3R)-3-(1-pyrrolidinylmethyl)-4-((1S)-5,6-dichloro-1-indancarbonyl)-tetrahydro-1,4-thiazine hydrochloride, in the second phase of the formalin test, a model of tonic pain, was examined in mice. R-84760 had a 2700 times more potent antinociceptive effect than morphine. The effect of R-84760 was antagonized by subcutaneously administered nor-binaltorphimine, a kappa-selective opioid receptor antagonist. Both intracerebroventricularly and intrathecally administered nor-binaltorphimine partially antagonized the antinociceptive effect of R-84760. Intrathecally administered phentolamine, an alpha-adrenoceptor **antagonist**, attenuated and desipramine, a **noradrenaline reuptake inhibitor**, augmented the antinociceptive effect of R-84760. Intrathecally administered noradrenaline attenuated the **nociceptive** response in the second phase of the formalin test. Intrathecally administered (+-)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), an N-methyl-D-aspartate (NMDA)-receptor antagonist, reduced and threo-beta-hydroxyaspartate, a reuptake inhibitor of glutamate, augmented the second phase nociceptive response. However, R-84760 did not influence the intrathecally injected NMDA-induced nociceptive response. These results suggest the following: R-84760 produces an extremely potent antinociceptive effect against tonic pain through the kappa-opioid receptors; the sites of action of subcutaneously administered R-84760 are the supraspinal and spinal loci in the central nervous system; and a part of the mechanism of the antinociceptive effect of R-84760 is activation of the descending noradrenergic pathway.

L11 ANSWER 35 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:306038 BIOSIS
DN PREV199497319038
TI Treatment of post-herpetic neuralgia: Antidepressants.

09/599,213

AU Max, Mitchell B.
CS National Inst. Health, Building 10, Room 3C-405, Bethesda, MD 20892 USA
SO Annals of Neurology, (1994) Vol. 35, No. SUPPL., pp. S50-S53.
ISSN: 0364-5134.
DT General Review
LA English
AB Five controlled clinical trials and extensive clinical experience have shown that amitriptyline and several other antidepressants reduce the severity of post-herpetic neuralgia. Studies in post-herpetic neuralgia and in **painful** diabetic neuropathy suggest that **blockade** of **norepinephrine reuptake** is the most important action accounting for **pain** relief; selective agents such as desipramine may be useful in patients unable to tolerate amitriptyline side effects. The selective serotonin reuptake inhibitors, zimelidine and paroxetine, have shown little effectiveness in neuropathic pain, but small studies in diabetic neuropathy have shown that paroxetine and citalopram have modest effects. Studies of the latter agents in post-herpetic neuralgia, concentration-response studies of amitriptyline, and studies of drug combinations including antidepressants may lead to improved treatment.

L11 ANSWER 36 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1994:10979 BIOSIS
DN PREV199497023979
TI **Inhibition** of spinal **noradrenaline uptake** by the centrally acting **analgesic** tramadol.
AU Hennies, H.-H.; Reimann, W.
CS Forschungszentrum, Gruenenthal GmbH, Zieglerstr. 6, 52078 Aachen Germany
SO Fundamental & Clinical Pharmacology, (1993) Vol. 7, No. 7, pp. 362.
Meeting Info.: Joint Meeting of the Deutsche Gesellschaft fuer Pharmakologie und Toxikologie (German Society for Pharmacology and Toxicology) and of the Association Francaise des Pharmacologistes (French Association of Pharmacologists) Lille, France October 6-8, 1993
ISSN: 0767-3981.
DT Conference
LA English

L11 ANSWER 37 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:504055 BIOSIS
DN PREV199396128062
TI Effects of the central analgesic tramadol and its main metabolite, O-demethyltramadol, on rat locus coeruleus neurones.
AU Sevcik, Jan; Nieber, Karen; Driessen, Bernd; Illes, Peter (1)
CS (1) Dep. Pharmacol., Univ. Freiburg, Hermann-Herder-Strasse 5, D-7800 Freiburg Germany
SO British Journal of Pharmacology, (1993) Vol. 110, No. 1, pp. 169-176.
ISSN: 0007-1188.
DT Article
LA English
AB 1 Tramadol is a centrally acting analgesic with low opioid receptor affinity and, therefore, presumably additional mechanisms of analgesic action. Tramadol and its main metabolite O-desmethyltramadol were tested on rat central noradrenergic neurones of the nucleus locus coeruleus (LC), which are involved in the modulation of nociceptive afferent stimuli. 2 In pontine slices of the rat brain the spontaneous discharge of action potentials of LC cells was recorded extracellularly. (-)-Tramadol (0.1-100 mu-M), (+)-tramadol (0.1-100 mu-M), (-)-O-desmethyltramadol (0.1-100 mu-M) and (+)-O-desmethyltramadol (0.01-1 mu-M) inhibited the firing rate in a concentration-dependent manner. (+)-O-desmethyltramadol had the highest potency, while all other agonists were active at a similar range of

concentrations. 3 (-)-Tramadol (10, 100 mu-M) was less inhibitory in brain slices of rats pretreated with reserpine (5mg kg-1, 5 h before decapitation) than in controls. 4 The effect of (-)-tramadol (10 mu-M) was abolished in the presence of the alpha-2-adrenoceptor antagonist, rauwolscine (1 mu-M), whilst that of (+)-O-desmethyltramadol (0.3 mu-M) virtually disappeared in the presence of the opioid antagonist, naloxone (0.1 mu-M). (+)-Tramadol (30 mu-M) and (-)-O-desmethyltramadol (10 mu-M) became inactive only in the combined presence of naloxone (0.1 mu-M) and rauwolscine (1 mu-M). 5 In another series of experiments, the membrane potential of LC neurones was determined with intracellular microelectrodes. (-)-Tramadol (100 mu-M) inhibited the spontaneous firing and hyperpolarized the cells; this effect was abolished by rauwolscine (1 mu-M). (+)-O-desmethyltramadol (10 mu-M) had a similar but somewhat larger effect on the membrane potential than (-)-tramadol. The (+)-O-desmethyltramadol- (10 mu-M) induced hyperpolarization was abolished by naloxone (0.1 mu-M). 6 The hyperpolarizing effect of noradrenaline (30 mu-M) was potentiated in the presence of (-)-tramadol (100 mu-M), but not in the presence of (+)-O-desmethyltramadol (10 mu-M). There was no potentiation of the noradrenaline (30 mu-M) effect, when the cells were hyperpolarized by current injection to an extent similar to that produced by (-)-tramadol (100 mu-M). 7 Both noradrenaline (100 mu-M) and (-)-tramadol (100 mu-M) decreased the input resistance. 8 The results confirm that the **analgesic** action of tramadol involves both opioid and non-opioid components. It appears that (-)-tramadol **inhibits** the **uptake** of **noradrenaline** and via a subsequent increase in the concentration of endogenous noradrenaline indirectly stimulates alpha-2-adrenoceptors. (+)0-desmethyltramadol seems to stimulate directly opioid mu-receptors. The effects of (+)-tramadol and (-)-O-desmethyltramadol consist of combined mu-opioid and alpha-2-adrenergic components.

L11 ANSWER 38 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:394171 BIOSIS
DN BA94:66346
TI ANALGESIC ORAL EFFICACY OF TRAMADOL HYDROCHLORIDE IN POSTOPERATIVE PAIN.
AU SUNSHINE A; OLSON N Z; ZIGHELBOIM I; DECASTRO A; MINN F L
CS ANALGESIC DEV. LTD., 907 FIFTH AVE., SUITE 1 EAST, NEW YORK, N.Y. 10021.
SO CLIN PHARMACOL THER, (1992) 51 (6), 740-748.
CODEN: CLPTAT. ISSN: 0009-9236.
FS BA; OLD
LA English
AB Tramadol hydrochloride is a synthetic opiate agonist with a plasma elimination half-life of 5 to 6 hours and peak plasma levels at about 1 1/2 hours. It derives its activity from attachment to the .mu.-receptor and **blockage** of **norepinephrine reuptake**. The purpose of this single-dose, double-blind, placebo-controlled study was to determine the **analgesic** effectivness of an oral administration of two dose levels of tramadol hydrochloride (75 or 150 mg) compared with the combination of 650 mg acetaminophen plus 100 my propoxyphene napsylate in 161 patients with severe postoperative pain after cesarean section. Analgesia was assessed over a 6-hour period. Treatments were compared on the basis of standard scales for pain intensity and relief and a number of derived variables based on these data. A global rating of the study medication was also used to compare treatments. The three active treatments were effective analgesics, statistically superior to placebo for many hourly and summary measures. A dose response was seen between the two tramadol doses, with the 150 mg dose providing significantly greater analgesia over the lower dose. The 75 mg dose of tramadol was generally more effective than the acetaminophen-propoxyphenic combination after hour 2, and significantly so for some hourly time points, as well as for the

globual rating of the medication. The 150 mg dose of tramadol was significantly more effective than the acetaminophene-propoxyphene combination from hour 2 through hour 6 for the sum of pain intensity differences and total pain relief scores, as well as for the global rating of the medication. Tramadol hydrochloride at both dose levels is an effective analgesic agent and at 150 mg is statistically superior to the acetaminophen-propoxyphene combination. No serious adverse effects were observed; however, dizziness was more frequently reported with 150 mg tramadol.

L11 ANSWER 39 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:330360 BIOSIS
DN BA94:32201
TI NEWER VERSUS OLDER ANTIDEPRESSANT DRUGS IN THE TREATMENT OF CHRONIC PAIN SYNDROMES.
AU DE ANGELIS L
CS INST. PHARMACOL., VIA A. VALERIO 32, UNIV. TRIESTE, 34127 TRIESTE, ITALY.
SO ADV THER, (1992) 9 (2), 91-97.
CODEN: ADTHE7.
FS BA; OLD
LA English
AB A substantial body of data documents the efficacy of antidepressant drugs in chronic pain syndromes. In this paper, we discuss the mechanism of the **analgesic** action of antidepressants and review the available data on newer antidepressants (**norepinephrine reuptake inhibitors**, serotonin **reuptake inhibitors** and agonists, nonreuptake **inhibitors**) in the treatment of chronic **pain** syndromes.

L11 ANSWER 40 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:330355 BIOSIS
DN BA94:32196
TI EFFECTS OF DESIPRAMINE AMITRIPTYLINE AND FLUOXETINE ON PAIN IN DIABETIC NEUROPATHY.
AU MAX M B; LYNCH S A; MUIR J; SHOAF S E; SMOLLER B; DUBNER R
CS NIDR/NIH PAIN RES. CLIN., NATL. INST. HEALTH, BUILD. 10, ROOM 3C-405, BETHESDA, MD. 20892.
SO N ENGL J MED, (1992) 326 (19), 1250-1256.
CODEN: NEJMAG. ISSN: 0028-4793.
FS BA; OLD
LA English
AB Background: Amitriptyline reduces the pain caused by peripheral-nerve disease, but treatment is often limited by side effects related to the drug's many pharmacologic actions. Selective agents might be safer and more effective. Methods: We carried out two randomized, double-blind, crossover studies in patients with **painful** diabetic neuropathy, comparing amitriptyline with the relatively selective **blocker** of **norepinephrine reuptake** desipramine in 38 patients, and comparing the selective blocker of serotonin reuptake fluoxetine with placebo in 46 patients. Fifty-seven patients were randomly assigned to a study as well as to the order of treatment, permitting comparison among all there drugs and placebo as the first treatment. The patients rated the degree of pain present each day using verbal descriptors, and they also assessed the extent of pain relief globally at the end of each treatment period. Results: After individual dose titration, the mean daily doses of the drugs were as follows: amitriptyline, 105 mg; desipramine, 111 mg; and fluoxetine, 40 mg. There was moderate or greater relief of pain in 28 of the 38 patients (74 percent) who received amitriptyline, 23 of the 38 patients (61 percent) who received desipramine, 22 of the 46 patients (48 percent) who received fluoxetine, and 19 of the 46 patients (41 percent)

who received placebo. The differences in responses between amitryptyline and desipramine and between fluoxetine and placebo were not statistically significant, but both amitriptyline and desipramine were superior to placebo. Amitriptyline and desipramine were as effective in patients who were not depressed as in depressed patients, but fluoxetine was effective only in depressed patients. Conclusions: Desipramine relieves pain caused by diabetic neuropathy with efficacy similar to that of amitriptyline, offering an alternative for patients unable to tolerate the latter. **Blockade** of **norepinephrine reuptake** is likely to mediate the **analgesic** effect of these antidepressant drugs in diabetic neuropathy. Fluoxetine, which blocks serotonin uptake, is no more effective than placebo for the relief of pain. (N Engl J Med 1992; 326-1250-6).

L11 ANSWER 41 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1992:227594 BIOSIS
DN BR42:109094
TI SINGLE DOSES OF DESIPRAMINE DO NOT POTENTIATE POSTOPERATIVE MORPHINE ANALGESIA.
AU ZEIGLER D; BENJAMIN J; CRAIG B E; LI S-H; SHOAF S E; MAX M B
CS NEUROBIOL. ANESTH. BRANCH, NIAAA, BETHESDA, MD.
SO NINETY-THIRD ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS, ORLANDO, FLORIDA, USA, MARCH 18-20, 1992. CLIN PHARMACOL THER. (1992) 51 (2), 146.
CODEN: CLPTAT. ISSN: 0009-9236.
DT Conference
FS BR; OLD
LA English

L11 ANSWER 42 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1991:300089 BIOSIS
DN BA92:21104
TI EFFICACY OF DESIPRAMINE IN PAINFUL DIABETIC NEUROPATHY A PLACEBO-CONTROLLED TRIAL.
AU MAX M B; KISHORE-KUMAR R; SCHAFER S C; MEISTER B; GRACELY R H; SMOLLER B; DUBNER R
CS NIDR/NIH PAIN RES. CLINIC, NATIONAL INST. HEALTH, BUILDING 10, ROOM 3C-405, BETHESDA, MD. 20892, USA.
SO PAIN, (1991) 45 (1), 3-10.
CODEN: PAINDB. ISSN: 0304-3959.
FS BA; OLD
LA English
AB Although amitriptyline relieves pain in many patients with painful diabetic neuropathy, side effects often preclude effective treatment. Desipramine has the least anticholinergic and sedative effects of the first generation tricyclic antidepressants. We compared a 6 week course of desipramine (mean dose, 201 mg/day) to active placebo in 20 patients with painful diabetic neuropathy in a double-blind crossover trial. Pain relief with desipramine was statistically significant in weeks 5 and 6. Eleven patients reported at least moderate relief with desipramine, compared to 2 with placebo. Pain relief tended to be greater in depressed patients, but relief was also observed in patients who did not show an antidepressant effect. We conclude that desipramine relieves **pain** in many patients with **painful** diabetic neuropathy, offering an alternative for patients unable to tolerate amitriptyline. **Blockade** of **norepinephrine reuptake**, an action shared by desipramine, amitriptyline, and other antidepressants proven effective in neuropathic **pain**, may mediate this **analgesic** effect.

L11 ANSWER 43 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1990:243402 BIOSIS
DN BA89:130355
TI DESIPRAMINE RELIEVES POSTHERPETIC NEURALGIA.
AU KISHORE-KUMAR R; MAX M B; SCHAFER S C; GANGHAN A M; SMOLLER B; GRACELY R H; DUBNER R
CS NIDR-NIH PAIN RES. CLINIC, NATL. INST. HEALTH, BUILDING 10, ROOM 3C-405, BETHESDA, MD. 20892.
SO CLIN PHARMACOL THER, (1990) 47 (3), 305-312.
CODEN: CLPTAT. ISSN: 0009-9236.
FS BA; OLD
LA English
AB Desipramine has the least anticholinergic and sedative effects of the first generation tricyclic antidepressant agents, but its pain-relieving potential has received little study. Other antidepressant agents-notably amitriptyline-are known to ameliorate postherpetic neuralgia, but those agents are often toxic. In a randomized double-blind crossover design, we gave 26 postherpetic neuralgia patients 6 weeks of treatment with desipramine (mean dose, 167 mg/day) and placebo. Nineteen patients completed both treatments; 12 reported at least moderate relief with desipramine and two reported relief with placebo. Pain relief with desipramine was statistically significant from weeks 3 to 6. Psychiatric interview at entry into the study produced a diagnosis of depression for 4 patients; pain relief was similar in depressed and nondepressed patients and was statistically significant in the nondepressed group alone. We conclude that desipramine administration relieves postherpetic neuralgia and that pain relief **is** not mediated by mood elevation. Blockade of **norepinephrine** reuptake, **an aciton** shared by desipramine, amitriptyline, and other antidepressant agents that have relieved neuropathic pain, may **be** involved in relief of postherpetic neuralgia.

L11 ANSWER 44 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1989:9248 BIOSIS
DN BA87:9248
TI A DOUBLE-BLIND RANDOMIZED STUDY OF CLOMIPRAMINE VERSUS MAPROTILINE IN PATIENTS WITH IDIOPATHIC PAIN SYNDROMES.
AU EBERHARD G; VON KNORRING L; NILSSON H L; SUNDEQUIST U; BJORLING G; LINDER H; SVARD K O; TYSK L
CS DEP. PSYCHIATRY, UMEA UNIV., S-901 85 UMEA, SWED.
SO NEUROPSYCHOBIOLOGY, (1988) 19 (1), 25-34.
CODEN: NPBYAL. ISSN: 0302-282X.
FS BA; OLD
LA English
AB Seventy patients with idiopathic syndromes were treated with maprotiline, a noradrenaline reuptake inhibitor, or clomipramine, a serotonin reuptake inhibitor in a 6-week, double-blind, randomized, multicenter trial. Fifty-two patients completed the double-blind phase. Overall, 50% of the patients improved. Significant decreases were seen not only in the levels of pain but also in bodily discomfort, sadness and inner tension (determined by visual analogue scales, VAS). A decrease was also found in the frequency of sleep disturbances, intellectual and emotional inhibition, irritability, guilt feelings, retardation, sadness and suicidal ideas (observed ratings). Sixty-three percent of the subjects showed an overall improvement during treatment with clomipramine as compared to 36% during treatment with maprotiline ($p < 0.05$). During clomipramine treatment significant decreases were seen on all the six VAS: sadness, bodily discomfort, inner tension, concentration of difficulties, memory disturbances and pain. Bodily discomfort and pain were significantly reduced during maprotiline treatment. The effects produced

by clomipramine were also significantly greater than the effects caused by maprotiline as concerns psychic anxiety and inhibition (VAS). The overall reduction in VAS was significantly greater than clomipramine when compared to maprotiline. The most important side effects were dry mouth (both drugs) and sweating (clomipramine). However, in the clomipramine group, 8 paients were excluded due to side effects as compared to 1 patient in the maprotiline group. Thus, the results indicate that antidepressants reduce not only pain but are also of clinical value in the treatment of patients with idiopathic pain syndromes. Drugs with pronounced effects on the serotonin reuptake are to be preferred.

L11 ANSWER 45 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1987:391393 BIOSIS
DN BR33:71533
TI **ANALGESIC** EFFECTS OF A NEW SEROTONIN-**NORADRENALINE** **UPTAKE INHIBITOR** RO-15-8081 IN COMPARISON WITH CODEINE AND PLACEBO ON EXPERIMENTALLY INDUCED **PAIN** IN HEALTHY MEN.
AU STACHER G; SCHNEIDER S; GAUPMANN G; ABATZI T; STACHER-JANOTTA G; MITTELBACH G
CS PSYCHOPHYSIOL. UNIT, UNIV. OF VIENNA, A-1090 VIENNA, AUSTRIA.
SO FIFTH WORLD CONGRESS ON PAIN, HAMBURG, WEST GERMANY, AUGUST 2-7, 1987. PAIN. (1987) 0 (SUPPL 4), S422.
CODEN: PAINDB. ISSN: 0304-3959.
DT Conference
FS BR; OLD
LA English

L11 ANSWER 46 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1985:327887 BIOSIS
DN BA79:107883
TI FLURADOLINE HP-494 A CENTRALLY ACTING ANALGESIC WITH ANTIDEPRESSANT PROPERTIES ANTIDEPRESSANT PHARMACOLOGY.
AU SPAULDING T; FIELDING S; CORNFELDT M; WILKER J; ELLIS D B; NOVICK W J; ONG H H
CS DEP. PHARMACOLOGY, HOECHST-ROUSSEL PHARMACEUTICALS INC., SOMERVILLE, NJ 08876.
SO DRUG DEV RES, (1985) 5 (3), 207-216.
CODEN: DDREDK. ISSN: 0272-4391.
FS BA; OLD
LA English
AB Fluradoline (HP 494), a tricyclic dibenz (b.f) oxepine derivative with an analgesic profile, was tested for antidepressant activity. After oral administration, fluradoline was twice as potent as imipramine and similar in potency to desmethylimipramine in blocking tetrabenazine-induced ptosis. Like standard antidepressants, fluradoline selectively increased response rates for electrical stimulation of the median forebrain bundle using internal capsule-lesioned rats. Response rates in nonlesioned rats were unaffected. There was partial protection against yohimbine toxicity and no potentiation of 5-hydroxytryptophan-induced seizures in mice. When administered to squirrel monkeys, the EEG profile from cortically-placed electrodes resembled that found for imipramine. In vivo and in vitro, fluradoline was not a monoamine oxidase **inhibitor**; however, the compound **blocked** the **reuptake** of **norepinephrine**, serotonin and dopamine in brain homogenates. In addition to the **analgesic** profile, there apparently is a concomitant antidepressant profile which may enhance the spectrum of activity of fluradoline.

L11 ANSWER 47 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1984:261242 BIOSIS

DN BA77:94226
TI SPINAL 5 HYDROXY TRYPTAMINE OR **NORADRENALINE UPTAKE INHIBITION** POTENTIATES SUPRA SPINAL MORPHINE ANTI **NOCICEPTION** IN RATS.
AU LARSEN J-J; ARNT J
CS DEP. PHARMACOL. TOXICOL., H. LUNDBECK CO. A/S, OTTILIAVEJ 7-9, DK-2500 COPENHAGEN, DENMARK.
SO ACTA PHARMACOL TOXICOL, (1984) 54 (1), 72-75.
CODEN: APTOA6. ISSN: 0001-6683.
FS BA; OLD
LA English
AB Spinal injection of the specific uptake inhibitor of 5-hydroxytryptamine (5-HT), citalopram, or of noradrenaline (NA) [norepinephrine], desipramine, potentiated the antinociception following intracerebroventricular injection of morphine in rats tested on the hot plate. Combined spinal injection of citalopram and desipramine caused a synergistic potentiation. The unselective and less potent inhibitor of both 5-HT and NA uptake, amitriptyline, did not cause potentiation. Both 5-HT and NA pathways are apparently involved in supraspinal morphine antinociception.

L11 ANSWER 48 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1982:203730 BIOSIS
DN BA73:63714
TI IN-VITRO BIOCHEMICAL EFFECTS OF NEFOPAM HYDRO CHLORIDE A NEW ANALGESIC AGENT.
AU TRESNAK-RUSTAD N J; WOOD M E
CS RIKER LAB. INC., 3M CENTER, ST. PAUL, MINN. 55144, USA.
SO BIOCHEM PHARMACOL, (1981) 30 (20), 2847-2850.
CODEN: BCPCA6. ISSN: 0006-2952.
FS BA; OLD
LA English
AB Nefopam hydrochloride (Acupan), an analgesic in rats and man, was a very weak inhibitor of [3H]naloxone binding (IC50 25 .mu.M) to brain homogenates in comparison to other **analgesic** agents. Nefopam was a potent **inhibitor** of synaptosomal **uptake** of dopamine, **norepinephrine** and serotonin, with IC50 values of 0.47, 0.89 and 0.34 .mu.M, respectively. The mechanism of **analgesic** action by nefopam probably is not related to direct actions on endogenous opiate receptors, but may be related to an enhancement of monoaminergic function by uptake inhibition.

L11 ANSWER 49 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1982:152638 BIOSIS
DN BA73:12622
TI EFFECT OF PSYCHOTROPIC SUBSTANCES AND NARCOTIC ANALGESIC DRUGS ON CARBON-14 LABELED NORADRENALINE UPTAKE BY SYNAPTOSOMES OF THE RAT CEREBRAL CORTEX.
AU MAISOV N I; TOLMACHEVA N S
CS LAB. NEUROCHEM. PHARMACOL., INST. PHARMACOL., ACAD. MED. SCI. USSR, MOSCOW, USSR.
SO FARMAKOL TOKSIKOL (MOSC), (1980) 43 (3), 302-306.
CODEN: FATOAO. ISSN: 0014-8318.
FS BA; OLD
LA Russian
AB The effect of different groups of neurotropic substances [Phenamine, cocaine, imipramine, clozapine, fentanyl, promedol, lemoran, azabutiron, trifluperidol, fluphenazine and dextromoramide] was studied on labeled noradrenaline [norepinephrine] and GABA uptake by synaptosomes of the rat brain cortex. Each group of the test compounds is characterized by

specific qualitative and quantitative features of the action on the above processes. Psychostimulants actively inhibit noradrenaline uptake without changing GABA uptake. Neuroleptics exert a pronounced **inhibitory** effect on GABA **uptake** and insignificantly **inhibit** **noradrenaline** accumulation. Antidepressants are very potent while narcotic **analgesic** drugs are less potent inhibitors of the accumulation of both neuromediators. Morphine and nalorphine have no effect no these processes.

L11 ANSWER 50 OF 78 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1978:86421 BIOSIS
DN BR15:29921
TI BIOLOGICAL ACTION OF SUBSTANCE P ITS DIFFERENTIATION BY AFFINITY AND INTRINSIC EFFICACY.
AU OEHME P; BERGMANN J; BIENERT M; HILSE H; PIESCHE L; MINH THU P; SCHEER E
SO VON EULER, ULF S. AND BENGT PERNOW (ED.). NOBEL SYMPOSIUM, 37. SUBSTANCE P. STOCKHOLM, SWEDEN, JUNE, 1976. XVI+344P. ILLUS. RAVEN PRESS: NEW YORK, N.Y., USA. (1977) 327-335.
ISBN: 0-89004-100-8.
FS BR; OLD
LA Unavailable

L11 ANSWER 51 OF 78 MEDLINE
AN 1999372808 MEDLINE
DN 99372808 PubMed ID: 10445636
TI Analgesics in ophthalmic practice: a review of the oral non-narcotic agent tramadol.
AU Gaynes B I; Barkin R L
CS Rush University, College of Medicine, Department of Ophthalmology, Chicago, Illinois 60612, USA.. bgaynes@rush.edu
SO OPTOMETRY AND VISION SCIENCE, (1999 Jul) 76 (7) 455-61. Ref: 36
Journal code: OIZ; 8904931. ISSN: 1040-5488.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014
AB This report reviews the causes of ocular pain and discusses the pharmacology, pharmacokinetics, efficacy, adverse effects, and dosage of tramadol, a novel non-narcotic oral analgesic. Tramadol is a synthetic analog of codeine with a dual mechanism of action that involves agonist activity at the mu opioid receptor, as well as **inhibition** of monoaminergic (**norepinephrine** and serotonin) **re-** **uptake**. Unlike opiate **analgesics**, tramadol has very low propensity toward physical dependence. Common dose-related adverse effects of tramadol include dizziness, nausea, vomiting, dry mouth, and/or drowsiness. Clinically, tramadol has been shown to be equivalent to acetaminophen (325 mg)-codeine (30 mg) combinations for the treatment of moderate or severe nonocular pain. Tramadol appears to be an effective analgesic agent for pain control due to postoperative surgical trauma, as well as in various chronic malignant and nonmalignant disease states. Tramadol has shown variable effectiveness in the control of pain related to dental procedures. The usefulness of tramadol in pain states from ophthalmic origin has yet to be clinically established.

L11 ANSWER 52 OF 78 MEDLINE
AN 1998433411 MEDLINE
DN 98433411 PubMed ID: 9760702
TI The effects of Aconitum alkaloids on the central nervous system.
AU Ameri A
CS Institute of Pharmacy and Pharmacology of Natural Compounds, University of Ulm, Germany.
SO PROGRESS IN NEUROBIOLOGY, (1998 Oct) 56 (2) 211-35. Ref: 136
Journal code: Q3R; 0370121. ISSN: 0301-0082.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 199811
ED Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981123
AB Preparations of Aconitum roots are employed in Chinese and Japanese medicine for analgesic, antirheumatic and neurological indications. The recent surge in use of phytomedicine derived from traditional Chinese medicine as well as increasing concerns about possible toxic effects of these compounds have inspired a great deal of research into the mechanisms by which certain Aconitum alkaloids may act on the central nervous system. The pharmacological effects of preparations of Aconitum roots are attributed to several diterpenoid alkaloids. The main alkaloid of these plants is aconitine, a highly toxic diterpenoid alkaloid which is known to suppress the inactivation of voltage-dependent Na+ channels by binding to neurotoxin binding site 2 of the alpha-subunit of the channel protein. In this article the pharmacology of several structurally related Aconitum alkaloids is highlighted and their therapeutic vs toxic potential is discussed. Neurochemical and neurophysiological studies will be reviewed with emphasis on the effects of the alkaloids in regions of the brain that have been implicated in pain transmission and generation of epileptic activity. Considering the chemical structure of the Aconitum alkaloids as well as their mechanism of action, a subdivision in three groups becomes obvious: the first group comprises such alkaloids which possess high toxicity due to two ester boundings at the diterpene skeleton. The members of this group activate voltage-dependent sodium channels already at resting potential and **inhibit noradrenaline reuptake**. Activation of sodium channels and in consequence excessive depolarization with final inexcitability and suppression of **pain** transmission account for their antinociceptive properties. The second group comprises less toxic monoesters which have been shown to possess strong antinociceptive, antiarrhythmic and antiepileptiform properties due to a blockade of the voltage-dependent sodium channel. Electrophysiological studies have revealed a use-dependent inhibition of neuronal activity by these alkaloids. They seem to be competitive antagonists of the group I-alkaloids. The third group of Aconitum alkaloids are lacking an ester side chain in the molecule. Toxicity is markedly reduced when compared with the two other groups. They fail to affect neuronal activity, but are reported to have antiarrhythmic actions suggesting that they may have different affinities to various subtypes of the alpha-subunit of the Na+ channel in brain and heart.

L11 ANSWER 53 OF 78 MEDLINE
AN 1998061489 MEDLINE
DN 98061489 PubMed ID: 9399121
TI Identification of tramadol and its metabolites in blood from drug-related

deaths and drug-impaired drivers.
AU Goeringer K E; Logan B K; Christian G D
CS Washington State Toxicology, Department of Laboratory Medicine, University of Washington, Seattle 98134, USA.
SO JOURNAL OF ANALYTICAL TOXICOLOGY, (1997 Nov-Dec) 21 (7) 529-37.
Journal code: K4R; 7705085. ISSN: 0146-4760.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980109
AB Tramadol is a centrally acting, binary analgesic that is neither an opiate-derived nor a nonsteroidal anti-inflammatory drug and that was approved for use in the United States in 1995. It is used to control moderate pain in chronic pain settings such as osteoarthritis and postoperative cases. Used in therapy as a racemic mixture, the (+)-enantiomer weakly binds to the mu-opioid receptor, and both enantiomers **inhibit** serotonin and **norepinephrine reuptake**. Tramadol's major active metabolite, O-desmethyltramadol (ODT), shows higher affinity for the mu-opioid receptor and has twice the **analgesic** potency of the parent drug. The synergism of these effects contributes to tramadol's analgesic properties with the (+)-enantiomer exhibiting 10-fold higher analgesic activity than the (-)-enantiomer. Although tramadol was initially thought to exhibit low abuse potential, Ortho-McNeil, the drug's manufacturer, recently reported a large number of adverse events attributed to tramadol including abuse by opioid-dependent patients, allergic reactions, and seizures. The high number of adverse reactions has prompted the company to update the prescribing information for the drug. An analytical method using gas chromatography-mass spectrometry (GC-MS) without derivatization for the determination of tramadol and its metabolites is reported. An n-butyl chloride extraction is followed by GC-MS analysis using a 5% phenylmethylsilicone column (30 m x 0.32-micron i.d.). Analysis of 12 blood samples from tramadol-related deaths and four nonfatal intoxications involving tramadol revealed concentrations ranging from 0.03 to 22.59 mg/L for tramadol, from 0.02 to 1.84 mg/L for ODT, and from 0.01 to 2.08 mg/L for N-desmethyltramadol. Three deaths were clearly attributable to acute morphine toxicity, one was a doxepin overdose, and six were multiple drug overdoses. The role of tramadol in each death is explored.

L11 ANSWER 54 OF 78 MEDLINE
AN 97369550 MEDLINE
DN 97369550 PubMed ID: 9235725
TI [Treatment of pain in oncology].
Il trattamento del dolore in oncologia.
AU De Conno F; Polastri D
CS Divisione di Terapia del Dolore e Cure Palliative, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
SO TUMORI, (1997) 83 (2 Suppl) S20-4. Ref: 49
Journal code: WJS; 0111356. ISSN: 0300-8916.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Italian
FS Priority Journals
EM 199707

ED Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970731

AB Basic guidelines for cancer pain treatment can be found in many different handbooks published in the last years. Particularly those of the World Health Organisation published in 1986 and revised in 1996, furnish useful indication for cancer pain treatment. The authors therefore focused on resuming the most recent development in this field. In the research regarding alternative routes of administration of opioids in alternative to the oral route, the rectal administration of morphine and methadone and the transdermal route for fentanyl have proved to be efficacious. The subcutaneous route (for morphine) as well as the intravenous, peridural and subaracnoid routes, being known for some time are not taken in consideration in this paper. Various studies suggest that alternative routes are necessary in 53-70% of patients in their last days or months of live. The most frequent causes for the need to stop oral administration are dysphagia, nausea, and uncontrollable vomiting, bowel obstruction, malabsorption, cognitive failure, coma, and pain syndromes requiring anaesthetics which need be administered via the spinal route. Among the drugs, tramadol seems to be effective in the control of moderate pain. Tramadol is a centrally acting **analgesic** drug; it has an agonist effect on mu 1 receptors of opioids and acts also by **inhibiting** the **re-uptake** of **noradrenaline** and serotonine which activates descending monoaminergic inhibitory pathways. Recent clinical studies revealed that pamidronate has an **analgesic** effect in **pain** due to bone metastasis. Pamidronate is part of the biphosphonates, which are active on bone metabolism and are usually being used for the treatment of hypercalcaemia in cancer. The authors also describe briefly the indication of ketamin in association with morphine for the treatment of neuropathic pain.

L11 ANSWER 55 OF 78 MEDLINE
AN 97274805 MEDLINE
DN 97274805 PubMed ID: 9190324
TI [Effectiveness and tolerance of tramadol in cancer pain. A comparative study with respect to buprenorphine].
Efficacite et tolerance du tramadol dans les douleurs neoplasiques. Etude comparative par rapport a la buprenorphine.
AU Bono A V; Cuffari S
CS Service d'Urologie, Hopital di Circolo, Varese, Italie.
SO DRUGS, (1997) 53 Suppl 2 40-9.
Journal code: EC2; 7600076. ISSN: 0012-6667.
CY New Zealand
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA French
FS Priority Journals
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB Opioid analgesics represent one of the most important tools in a sequential pharmacological approach to oncological pain relief. They are recommended by the WHO when nonsteroidal anti-inflammatory drugs (NSAIDs) no longer provide adequate analgesia. However, the use of opioids is limited because of their numerous and often severe adverse effects. This aspect of opioids has motivated continuous research projects aimed at discovering drugs that can provide maximum pain relief but with improved tolerability. Tramadol is a new, centrally acting analgesic with a dual

mechanism of action. It shows a selective interaction with mu receptors, which are responsible for **nociception**, and has weak pharmacodynamic activity on other opioid receptors. At the same time, it acts synergistically on neuroamine transmission by **inhibiting** synaptic **noradrenaline** (**norepinephrine**) **reuptake** and inducing intrasynaptic serotonin (5-hydroxytryptamine; 5-HT) release. From a pharmacokinetic standpoint, tramadol offers high bioavailability, with similar patterns after oral or parenteral administration (half-life 5 to 7 hours, time to peak plasma concentration 3.1 hours, and approximately 20% plasma protein binding). Although the efficacy of tramadol is comparable to that of other drugs with similar modes of action, the incidence of side effects such as constipation and respiratory depression is lower. The frequency of euphoria and dysphoria is negligible, resulting in little risk of abuse or dependence. It therefore seemed appropriate to further investigate the efficacy and tolerability of tramadol, defined as having only weak potency, in comparison with a widely used opioid, in oncological pain. Buprenorphine was selected as an opioid with a potency equivalent to half that of morphine, but with tolerability that is partially limited by the fact that it frequently gives rise to adverse reactions considered typical of stronger opioids. To compare the analgesic effect and tolerability of tramadol and buprenorphine, 60 patients (44 men, 16 women; average age 61.4 years), all presenting with advanced tumours, were treated orally in a controlled crossover trial with randomised sequences. Patients took both drugs, each for a week, with a 24-hour washout period between treatments. Tramadol was prescribed at the daily dose of 300mg, orally, and buprenorphine at 0.6 mg/day, as a sublingual preparation. Assessments were made of Karnofsky performance status and severity of pain before and during the 4 hours after taking the 2 drugs. Each patient also completed a daily diary recording the severity of pain 1 hour after the dose, the evolution of pain during the day and its severity compared with that on the previous day. They also assessed the duration and quality of sleep. The Karnofsky index changed little with either treatment, but all other variables showed worthwhile improvement, indicating the significant analgesic effect of both drugs. Buprenorphine and tramadol had a similar analgesic effect, although the improvement with the test drug was significant within 1 hour of administration ($p < 0.05$ compared with baseline) and more marked ($p < 0.05$ on day 2 compared with buprenorpine). At the end of tramadol treatment, sleep had also improved, both quantitatively and qualitatively (both $p < 0.05$). The final assessment was significantly in favour of tramadol as regards efficacy ($p < 0.05$) and patient acceptability ($p < 0.01$). Thus, tramadol was better tolerated than buprenorphine, and caused fewer and milder adverse reactions. Only 1 patient discontinued tramadol, compared with 18 using reference therapy. Tramadol, although theoretically less potent, nevertheless brought about as much pain relief as the comparator opioid. In conclusion, for this class of drug, tramadol provides an excellent balance between efficacy and tolerability, confirming preliminary studies.

L11 ANSWER 56 OF 78 MEDLINE
AN 97274804 MEDLINE
DN 97274804 PubMed ID: 9190323
TI [Treatment of post-herpes zoster pain with tramadol. Results of an open pilot study versus clomipramine with or without levomepromazine]. Traitement des douleurs post-zosteriennes par le tramadol. Resultats d'une etude pilote ouverte versus clomipramine avec ou sans levomepromazine.
AU Gobel H; Stadler T
CS Service de Neurologie, Hopital Universitaire, Kiel, Allemagne.
SO DRUGS, (1997) 53 Suppl 2 34-9.
Journal code: EC2; 7600076. ISSN: 0012-6667.

09/599,213

CY New Zealand
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA French
FS Priority Journals
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 19990129
Entered Medline: 19970619

AB To date, no universally applicable recommendations are available for the treatment of patients with postherpetic neuralgia. A mixture of clinical anecdotes, experimental findings and observations from clinical trials form the basis of the medical arsenal for this condition. Tricyclic antidepressants are commonly used, and clinical experience and several investigations have documented their effectiveness. Today, single entity antidepressants, which can be combined with neuroleptics to increase analgesia, are generally recommended for the treatment of postherpetic neuralgia. Some authors also recommend the additional administration of an opioid if analgesia is inadequate. Just over a decade ago, opioids were considered ineffective for the treatment of neuropathic pain; however, more recent investigations relating to the use of opioids, primarily in the treatment of nontumour-related chronic pain, have led to a revision of their use in neuropathic pain. Nevertheless, the use of opioid therapy for neurogenic pain remains controversial. Tramadol is a synthetic, centrally acting **analgesic** with both opioid and nonopioid **analgesic** activity. The nonopioid component is related to the **inhibition** of **noradrenaline** (**norepinephrine**) **reuptake** and stimulation of serotonin (5-hydroxytryptamine; 5-HT) release at the spinal level. In this regard, there are parallels with antidepressants, which are believed to potentiate the effect of biogenic amines in endogenous pain-relieving systems. There is evidence that, in tramadol, both mechanisms act synergistically with respect to analgesia. The aim of this pilot study was to investigate, for the first time, the analgesic efficacy and tolerability of tramadol, compared with the antidepressant clomipramine, in the treatment of postherpetic neuralgia. If necessary, clomipramine was used in combination with the neuroleptic levomepromazine. The study allowed individualised dosages at predetermined intervals up to a maximum daily dose of tramadol 600mg and clomipramine 100mg, or clomipramine 100mg with or without levomepromazine 100mg. 21 (60%) of 35 randomised patients (> or = 65 years) received the study medication over the 6-week period [tramadol n = 10; clomipramine with or without levomepromazine) n = 11]. After 3 weeks' treatment the dosage in both groups remained almost constant for the rest of the 6-week treatment phase (mean daily dose: tramadol 250 to 290mg; clomipramine 59.1 to 63.6mg). Only 3 patients required the combination of clomipramine and levomepromazine. At the outset, both groups recorded an average pain level of 'moderate' to 'very severe'. In correlation with increasing the study medication, this had decreased to 'slight' by the end of the treatment, when 9 of 10 patients in the tramadol group and of 6 of 11 patients in the clomipramine group retrospectively rated their analgesia as excellent, good or satisfactory. The psychological/physical condition of the patients did not change significantly during tramadol treatment. Sensitivity and depression parameters decreased in the clomipramine group. The incidence of adverse events for all patients was similar in both groups (tramadol 76.5%; clomipramine with or without levomepromazine 83.3%). In conclusion, tramadol would appear to be an interesting therapeutic alternative for pain relief in postherpetic neuralgia, particularly in patients who are not depressed. In clinical practice, tramadol and clomipramine can best be used differentially. For example, tramadol could be the drug of first

choice in patients with obvious cardiovascular disease (not an uncommon problem in the > or = 65 year age group) in whom antidepressants are contraindicated, and similarly in patients in whom an antidepressant effect is not required. (ABSTRACT TRUNCATED)

L11 ANSWER 57 OF 78 MEDLINE
AN 97274802 MEDLINE
DN 97274802 PubMed ID: 9190321
TI [Pharmacology of tramadol].
Pharmacologie du tramadol.
AU Dayer P; Desmeules J; Collart L
CS Service de Pharmacologie Clinique et Consultation de la Douleur, Hopital Cantonal Universitaire, Geneve, Suisse.
SO DRUGS, (1997) 53 Suppl 2 18-24. Ref: 39
Journal code: EC2; 7600076. ISSN: 0012-6667.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619
AB (+/-)-Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors. Its selectivity for mu receptors has recently been demonstrated, and the M1 metabolite of tramadol, produced by liver O-demethylation, shows a higher affinity for opioid receptors than the parent drug. The rate of production of this M1 derivative (O-demethyl tramadol), is influenced by a polymorphic isoenzyme of the debrisoquine-type, cytochrome P450 2D6 (CYP2D6). Nevertheless, this affinity for mu receptors of the CNS remains low, being 6000 times lower than that of morphine. Moreover, and in contrast to other opioids, the analgesic action of tramadol is only partially inhibited by the opioid antagonist naloxone, which suggests the existence of another mechanism of action. This was demonstrated by the discovery of a monoaminergic activity that inhibits noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) reuptake, making a significant contribution to the analgesic action by blocking nociceptive impulses at the spinal level. (+/-)-Tramadol is a racemic mixture of 2 enantiomers, each one displaying differing affinities for various receptors. (+/-)-Tramadol is a selective agonist of mu receptors and preferentially inhibits serotonin reuptake, whereas (-)-tramadol mainly **inhibits noradrenaline reuptake**. The action of these 2 enantiomers is both complementary and synergistic and results in the **analgesic** effect of (+/-)-tramadol. After oral administration, tramadol demonstrates 68% bioavailability, with peak serum concentrations reached within 2 hours. The elimination kinetics can be described as 2-compartmental, with a half-life of 5.1 hours for tramadol and 9 hours for the M1 derivative after a single oral dose of 100mg. This explains the approximately 2-fold accumulation of the parent drug and its M1 derivative that is observed during multiple dose treatment with tramadol. The recommended daily dose of tramadol is between 50 and 100mg every 4 to 6 hours, with a maximum dose of 400 mg/day; the duration of the analgesic effect after a single oral dose of tramadol 100mg is about 6 hours. Adverse effects, and nausea in particular, are dose-dependent and therefore considerably more likely to appear if the loading dose is high. The reduction of this dose during the first days of treatment is an important factor in improving tolerability. Other adverse effects are

generally similar to those of opioids, although they are usually less severe, and can include respiratory depression, dysphoria and constipation. Tramadol can be administered concomitantly with other analgesics, particularly those with peripheral action, while drugs that depress CNS function may enhance the sedative effect of tramadol. Tramadol should not be administered to patients receiving monoamine oxidase inhibitors, and administration with tricyclic antidepressant drugs should also be avoided. Tramadol has pharmacodynamic and pharmacokinetic properties that are highly unlikely to lead to dependence. This was confirmed by various controlled studies and postmarketing surveillance studies, which reported an extremely small number of patients developing tolerance or instances of tramadol abuse. Tramadol is a central acting analgesic which has been shown to be effective and well tolerated, and likely to be of value for treating several pain conditions (step II of the World Health Organization ladder) where treatment with strong opioids is not required.

L11 ANSWER 58 OF 78 MEDLINE
AN 97229930 MEDLINE
DN 97229930 PubMed ID: 9075493
TI Tramadol: a new centrally acting analgesic.
AU Lewis K S; Han N H
CS Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, Downers Grove, IL 60515, USA.. klewis@rush.edu
SO AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (1997 Mar 15) 54 (6) 643-52.
Ref: 68
Journal code: CBH; 9503023. ISSN: 1079-2082.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971119
AB The pharmacology, pharmacokinetics, efficacy, adverse effects, and dosage and administration of tramadol are reviewed. Tramadol is a synthetic analogue of codeine that binds to mu opiate receptors and **inhibits norepinephrine** and serotonin **reuptake**. It is rapidly and extensively absorbed after oral doses and is metabolized in the liver. **Analgesia** begins within one hour and starts to peak in two hours. In patients with moderate postoperative pain, i.v. or i.m. tramadol is roughly equal in efficacy to meperidine or morphine; for severe acute pain, tramadol is less effective than morphine. Oral tramadol can also be effective after certain types of surgery. Tramadol and meperidine are equally effective in postoperative patient-controlled analgesia. In epidural administration for pain after abdominal surgery, tramadol is more effective than bupivacaine but less effective than morphine. In patients with ureteral calculi, both dipyrone and butylscopolamine are more effective than tramadol. For labor pain, i.m. tramadol works as well as meperidine and is less likely to cause neonatal respiratory depression. Oral tramadol is as effective as codeine for acute dental pain. In several types of severe or refractory cancer pain, tramadol is effective, but less so than morphine; for other types of chronic pain, such as low-back pain, oral tramadol works as well as acetaminophen-codeine. Common adverse effects of tramadol include dizziness, nausea, dry mouth, and sedation. The abuse potential seems low. The recommended oral dosage is 50-100 mg every four to six hours. Tramadol is an effective, if expensive,

alternative to other analgesics in some clinical situations.

L11 ANSWER 59 OF 78 MEDLINE
AN 93163642 MEDLINE
DN 93163642 PubMed ID: 1287107
TI Effects of a single oral dose of desipramine on postoperative morphine analgesia.
AU Max M B; Zeigler D; Shoaf S E; Craig E; Benjamin J; Li S H; Buzzanell C; Perez M; Ghosh B C
SO JOURNAL OF PAIN AND SYMPTOM MANAGEMENT, (1992 Nov) 7 (8) 454-62.
Journal code: IJJ; 8605836. ISSN: 0885-3924.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Nursing Journals
EM 199303
ED Entered STN: 19930402
Last Updated on STN: 19930402
Entered Medline: 19930318
AB Drugs that **block norepinephrine reuptake** offer promise as opioid potentiators, because norepinephrine mediates opioid **analgesia** but not side effects such as sedation or nausea. In a two-by-two factorial design, we randomized 62 inpatients with pain following major surgery to receive either desipramine, 50 mg by mouth, or placebo at 6 a.m. on the first day after surgery. At their first request of pain medication after 8 a.m., they were given intravenous morphine, either 0.033 mg/kg or 0.10 mg/kg. Pain relief and side effects were assessed for 4 hr; peak relief on the visual analog scale (VAS) was the primary outcome variable. Pain relief, side effect scores, and time to remedication were significantly greater with the higher dose than with the lower dose of morphine, verifying assay sensitivity, but desipramine pretreatment did not significantly enhance morphine analgesia. The mean increase in peak VAS relief score after desipramine pretreatment, relative to placebo, was 6%; the 95% confidence interval for this estimate ranged from a 21% reduction to a 34% increase in pain relief. These results differ from a previous report that 1 week of pretreatment with desipramine, 75 mg per day, potentiated postoperative morphine analgesia. We conclude that if desipramine potentiation of opioid analgesia occurs in humans, its demonstration may require higher doses or chronic treatment.

L11 ANSWER 60 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-04003 DRUGU T
TI Safety issues in the pharmacologic management of chronic pain in the elderly.
AU Shimp L A
CS Univ.Michigan
LO Ann Arbor, Mich., USA
SO Pharmacotherapy (18, No. 6, 1313-22, 1998) 1 Fig. 1 Tab. 74 Ref.
CODEN: PHPYDQ ISSN: 0277-0008
AV College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109-1065, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The safety issues involved in the pharmacological management of pain in the elderly are reviewed with reference to prevelance of pain, types of pain, treatment and drug therapy with acetaminophen, NSAIDs, traditional

opioid analgesics, tramadol, and antidepressants. Given the frequently prolonged duration of therapy, optimal management requires minimizing the risk of adverse effects.

L11 ANSWER 61 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-30234 DRUGU T
TI Remifentanil and tramadol.
AU Duthie D J R
CS Univ.Leicester
LO Leicester, U.K.
SO Br.J.Anaesth. (81, No. 1, 51-57, 1998) 2 Fig. 58 Ref.
CODEN: BJANAD ISSN: 0007-0912
AV Department of Anaesthesia, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, England.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The clinical use of remifentanil (Ultiva, Glaxo-Wellcome) and tramadol (Zydol, Zamadol, ASTA) in the treatment of pain are reviewed with reference to their mode of action, adverse effects, dosage, and pharmacokinetics. Remifentanil is a rapidly metabolized opioid agonist used during the induction and maintenance of anesthesia. Tramadol is a **norepinephrine uptake inhibitor** which regulates **pain** by an unknown mechanism and is used in the management of postoperative **pain**. Tramadol and remifentanil act by very different mechanisms but both analgesics are effective in varying clinical situations.

L11 ANSWER 62 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-08811 DRUGU P
TI Antinociceptive effects of monoamine reuptake inhibitors administered alone or in combination with mu opioid agonists in rhesus monkeys.
AU Gatch M B; Negus S; Mello N K
CS Harvard-Med.Sch.
LO Belmont, Mass.
SO Psychopharmacology(Berlin) (135, No. 1, 99-106, 1998) 3 Fig. 1 Tab. 51 Ref.
CODEN: PSCHDL ISSN: 0033-3158
AV Department of North Texas, Health Science Center at Forth Worth, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107-2699, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The antinociceptive effects of the serotonin reuptake inhibitors, clomipramine HCl (Research-Biochem.) and fluoxetine HCl (Lilly) administered i.m. alone or in combination with the mu opioid agonists, nalbuphine HCl (Research-Biochem.) and morphine sulfate both s.c. were investigated in monkeys. Clomipramine and fluoxetine produced weak antinociceptive effects, antagonized by the serotonin receptor antagonist i.m. mianserin HCl, and enhanced the antinociceptive effects of nalbuphine and morphine. The **norepinephrine reuptake inhibitors**, nisoxetine and tomoxetine, and the dopamine reuptake inhibitors, bupropion and GBR-12909 had little or no effect on **nociception**. The results suggest that the antinociceptive effects of cocaine may be mediated by serotonergic systems and serotonin reuptake inhibitors may prove to be useful adjuncts to opioids in the treatment of pain.

L11 ANSWER 63 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-07047 DRUGU P
TI Alpha2-adrenergic mechanisms of analgesia: strategies of improving their therapeutic window and identification of the novel, potent alpha2A-adrenergic receptor agonist, S 18616.
AU Millan M J
LO Paris, Fr.
SO Adv.Pharmacol. (42, 575-79, 1998) 6 Ref.
CODEN: ADPHEL ISSN: 1054-3589
AV Department of Psychopharmacology, Institut de Recherches Servier, 78290 Croissy-sur-Seine, Paris, France.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The alpha-2A adrenergic agonist S-18616 is briefly reviewed. Low-dose S-18616 is analgesic s.c. and p.o. in the formalin paw-lick test in mice. S-18616 is sedative at higher doses, but it appears to show a better separation of antinociceptive from sedative properties than do clonidine or dexmedetomidine. Alpha-2A adrenoceptors predominate in the dorsal horn of the spinal cord, and are known to be important mediators of antinociception. Several possible strategies for improving the therapeutic window of analgesic alpha-2A agonists are discussed.

L11 ANSWER 64 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1997-46858 DRUGU T
TI Imipramine for sphincter of Oddi dysfunction (SOD): A placebo-controlled randomized pilot study.
AU Desautels S; Slivka A; Chun A; Holeva K; DiLorenzo C; Wald A
CS Univ.Pittsburgh
LO Pittsburgh, Pa., USA
SO Am.J.Gastroenterol. (92, No. 9, 1633, 1997) 1 Tab. 2 Ref.
CODEN: AJGAAR ISSN: 0002-9270
AV University of Pittsburgh, Pittsburgh, PA, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB Imipramine (IMI) reduces episodes of **pain** in patients with non-cardiac chest **pain** independent of psychological profiles. This may result from **blockade** of **norepinephrine re-uptake** and enhancement of **inhibitory** action of descending **pain**-modulating neurons. The Authors previously reported that duodenal specific hyperalgesia occurs in patients with SOD. This placebo-controlled study in 8 patients investigated whether IMI improves pain in SOD types II and III. IMI improved objective symptoms in some patients. Those with objective improvement exhibited no baseline psychological distress. IMI at 50 mg qhs did not improve psychological profiles. The response of IMI may be influenced by psychological profiles in patients with SOD. (conference abstract).

L11 ANSWER 65 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1995-10789 DRUGU P
TI Newer antidepressants: analgesia and relative monoamine reuptake inhibitory potency.
AU Rafieian Kopaei M; Sewell R D E
LO Cardiff, U.K.
SO J.Pharm.Pharmacol. (46, Suppl. 2, 1088, 1994) 1 Tab. 5 Ref.
CODEN: JPPMAB ISSN: 0022-3573

AV Welsh School of Pharmacy, UWCC, King Edward VII Avenue, Cardiff CF1 3XF, Wales.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The relationship between the analgesic activity of the new 5-HT specific reuptake inhibitor antidepressants citalopram (CIT), fluoxetine (FLX), zimelidine (ZMD), fluvoxamine (FLV), paroxetine (PRX) and sertraline (STR) in mice following s.c. administration and in-vitro **inhibition** of 5-HT, **noradrenaline** and dopamine **reuptake** was studied. All compounds produced linear log dose-**analgesic** responses; however, Spearman's rho correlation coefficients between **analgesia** and 5-HT, noradrenaline and dopamine uptake were -0.54, -0.54 and -0.43, respectively, suggesting no overall rank correlation between the parameters following acute administration. The results suggest that other pharmacological properties such as opioid-like activity or diversity of pharmacokinetic characteristics may disrupt any straightforward correlation between monoamine uptake and analgesia. (conference abstract).

L11 ANSWER 66 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-23620 DRUGU T S
TI The pharmacology of tramadol.
AU Dayer P; Collart L; Desmeules J
CS Univ.Geneva
LO Geneva, Switzerland
SO Drugs (47, No. 1, Suppl. 1, 03-07, 1994) 3 Fig. 24 Ref.
CODEN: DRUGAY ISSN: 0012-6667
AV Division of Clinical Pharmacology and Pain Clinic, Geneva University Hospital, CH-1211 Geneva, Switzerland.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The pharmacology of tramadol (TM) is reviewed with special reference to its mechanism of action, its pharmacokinetics and its clinical efficacy and safety as a central analgesic of intermediate potency. The dual mechanism of action of TM may contribute both to the delayed emergence of tolerance during its long-term administration and to its efficacy in certain chronic pain conditions such as neuropathic pain. (congress).

L11 ANSWER 67 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1994-20215 DRUGU P
TI Both enantiomers participate in the antinociceptive effect of tramadol.
AU Nagelschmitz J; Hoffmann K; Gerloff J; Kobal G
CS Gruenenthal; Univ.Erlangen
LO Aachen, Erlangen, Germany,West
SO Arch.Pharmacol. (349, Suppl., R144, 1994)
CODEN: NSAPCC ISSN: 0028-1298
AV Department of Clinical Pharmacology, Gruenenthal GmbH Center of Research, Zieglerstrasse 6, D-52078 Aachen; Germany.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB Tramadol (T) consists of 2 enantiomers with distinct pharmacologic **analgesic** properties. The opioid activity and a weaker serotonergic activity reside in the (+)-enantiomer; the (-)-enantiomer exhibits mainly **noradrenaline re-uptake**

inhibition and also serotonergic activity. T was compared with (+)-T and (-)-T, each given as a total infusion dose of 200 mg, in a double-blind, randomized, 4-way, placebo (P)-controlled, crossover study in 20 healthy male volunteers. Both enantiomers of T are effective analgesics. The non-opioid enantiomer cannot be considered "enantiomeric ballast". A sedative effect is attributed to the opioid moiety, which is not present in the racemate and the (-)-T. (congress abstract).

L11 ANSWER 68 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1991-26239 DRUGU P
TI Involvement of the Serotonergic System in the Antinociceptive Effects of Tramadol.
AU Driessen B; Schleutz H; Reimann W
CS Gruenenthal
LO Aachen, Germany,West
SO Arch.Pharmacol. (343, Suppl., R101, 1991) 1 Ref.
CODEN: NSAPCC ISSN: 0028-1298
AV Gruenenthal GmbH, Department of Pharmacology, Zieglerstrasse 6, D-5100 Aachen, Germany.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The Authors investigated whether tramadol has a serotonergic component in its analgesic mode of action in studies on isolated rat frontal cortex and in studies on rats in-vivo (drugs given intrathecally). Nitroquipazine (DU-24565) and zimeldine were also used in-vitro, and intrathecal morphine, intrathecal desipramine and i.p. ritanserin were also used in-vivo. Results provided evidence that tramadol enhances the extraneuronal serotonin concentration by displacement of intraneuronal serotonin. This indirect mimetic action seems to be of relevance in-vivo since antinociceptive effects of tramadol were specifically antagonized by the serotonin antagonist ritanserin. (congress abstract).

L11 ANSWER 69 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1987-44302 DRUGU C P
TI Tazadolene Succinate: A Structurally Novel Non-Opioid Analagesic with Antidepressant Properties.
AU Vonvoigtlander P E; Chidester C G; Kane M P; Szmuszkovicz J
CS Upjohn
LO Kalamazoo, Michigan, United States
SO Drug Des.Delivery (1, No. 2, 103-08, 1986) 1 Fig. 2 Tab. 14 Ref.
CODEN: DDDEEJ
AV Research Laboratories, The Upjohn Company, Kalamazoo, MI 49001, U.S.A.
LA English
DT Journal
FA AB; LA; CT; MPC
FS Literature
AB The synthesis and pharmacology of tazadolene succinate (TZ) and p-hydroxy-TZ (HTZ) were reported. X-ray structure of TZ was determined.Both were potent **analgesics** (s.c. in rats), and like imipramine potentiated yohimbine, and antagonized oxotremorine s.c. in mice, and **inhibited** the **uptake** of 3H-**noradrenaline** and 3H-5-HT in vitro. The **analgesic** activity was not blocked by naloxone. TZ is a racemate; neither of the enantiomers was as active as the racemate.

L11 ANSWER 70 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1987-33855 DRUGU P
TI **Analgesic** Effects of a New Serotonin/**Noradrenaline**

Uptake Inhibitor (Ro 15-8081) in Comparison with Codeine and Placebo on Experimentally Induced **Pain** in Healthy Men.

AU Stacher G; Schneider S; Gaupman G; Abatzi T; Stacher Janotta G; Mittelbach G

LO Vienna, Austria

SO Pain (Suppl. 4, S442, 1987)
CODEN: PAINDB ISSN: 0304-3959

AV Psychophysiology Unit, University of Vienna, A-1090 Vienna, Austria.

LA English

DT Journal

FA AB; LA; CT; MPC

FS Literature

AB RO-15-8081 (Roche) produced marked increases in threshold and tolerance to electrically induced pain and of the threshold to thermally induced cutaneous pain in 20 healthy men, in a randomized, double-blind, placebo, controlled study. The maximum effects of RO-15-8081 were comparable to those of codeine (C), and the occurrence of side effects was only slightly higher than that with placebo. It is concluded that RO-15-8081 alleviates electrically and thermally induced pain, and thus has a potential clinical use. (congress abstract).

L11 ANSWER 71 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1983-42423 DRUGU P

TI Depression of Spinal NE Uptake by Ketamine and its Isomers: Possible Relationship to Analgesia and Skeletal Muscle Hypertonicity.

AU Lundy P; Jones D J

LO San Antonio, Texas, United States

SO Anesthesiology (59, No. 3A, A383, 1983) 2 Fig. 4 Ref.
CODEN: ANESAV ISSN: 0003-3022

AV Department of Anesthesiology, The University of Texas Health Science Center, San Antonio, Texas, U.S.A.

LA English

DT Journal

FA AB; LA; CT

FS Literature

AB Ketamine (KET) competitively **inhibited noradrenaline** (NA) **uptake** by synaptosomes from rat spinal cord and cortex, which may account for modulation of **pain** transmission. Both KET(+) and KET(-) blocked NA uptake in a manner consistent with their effects on peripheral nerve. Phencyclidine (P) also inhibited NA uptake. Inhibition of NA uptake at synapses may account for KET-induced skeletal muscle hypertonicity. (congress).

L11 ANSWER 72 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1983-40245 DRUGU P

TI Differential Interactions of Four Antidepressants with Opiate and Non -Opiate Induced Antinociception.

AU Gonzalez J P; Sewell R D E; Spencer P S J

LO Cardiff, United Kingdom

SO Br.J.Pharmacol. (80, No. 1, Suppl., 560P, 1983) 4 Ref.
CODEN: BJPCBM ISSN: 0007-1188

AV Division of Pharmacology, The Welsh School of Pharmacy, UWIST, Cardiff, CF1 3NU, U.K.

LA English

DT Journal

FA AB; LA; CT

FS Literature

AB The effects of (+) oxaprotiline (+OXA), nomifensine (NOM), clomipramine (CLOM) and mianserin (MIAN) on the analgesic effects of morphine,

etorphine, 2-D-Ala, 5-D-Leu enkephalin (DADL), clonidine and oxotremorine were studied in mice. (congress abstract).

L11 ANSWER 73 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1983-36863 DRUGU P B E
TI Biochemical Effects of Carbamazepine: Relationship to its Mechanisms of Action in Affective Illness.
AU Post R M; Uhde T W; Rubinow D R; Ballenger J C; Gold P W
LO Bethesda, Maryland, United States
SO Progr.NeuroPsychopharmacol.Biol.Psychiatry (7, No. 2-3, 263 -71, 1983) 67 Ref. ISSN: 0278-5846
AV Biological Psychiatry Branch, NIMH Room 3N212, Building 10, 9000 Rockville Pike, Bethesda, MD 20205, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB The therapeutic effects of carbamazepine (C) in affective illness in addition to its antiepileptic effects, are reviewed together with its biochemical actions on neurotransmitter systems in comparison with lithium, tricyclic antidepressants and neuroleptics. C is efficacious in lithium-resistant manic depressive illness and schizoaffective disorder. C alters activity at gamma aminobutyric acid (GABA) receptors, the adenosine receptor and on cAMP but does not inhibit binding at dopamine, opiates, muscarinic cholinergic or beta adrenergic receptors. It is hoped that the actions of C may enable elucidation of mechanisms underlying affective disorders.

L11 ANSWER 74 OF 78 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1983-04944 DRUGU T
TI The Use of Psychotropic Drugs in the Treatment of Chronic Pains.
AU Kocher R
LO Basle, Switzerland
SO Schweiz.Rundsch.Med.Prax. (71, No. 45, 1790-94, 1982) 3 Fig. 5 Ref. CODEN: SRMPDJ ISSN: 0369-8394
AV FMH Neurologie, Psychiatrische Universitaetskinik, Wilhelm-Klein-Strasse 27, 4025 Basel, Switzerland.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AB The use of psychotropic drugs in the treatment of chronic pain is reviewed. In particular carbamazepine (C) antidepressants and neuroleptics have improved treatment by their analgesic effect and potentiation and economization of analgesics without development of drug dependence. Some neuroleptics (e.g. haloperidol) bind to opiate receptors resulting in opiate antagonism.

L11 ANSWER 75 OF 78 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95210493 EMBASE
DN 1995210493
TI Focus on trmadol: A centrally acting analgesic for moderate to moderately severe pain.
AU Barkin R.L.
CS St. Luke's Medical Center,Chicago, IL, United States
SO Formulary, (1995) 30/6 (321-325).
ISSN: 0098-6909 CODEN: FORMF
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery

030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Tramadol is an atypical centrally acting binary **analgesic** with a dual mechanism of action. The drug occupies opioid receptors and **inhibits** the **reuptake** of **norepinephrine** and serotonin. Compared with other centrally acting opioids, tramadol is associated with a lower degree of respiratory depression, less tolerance, and less abuse potential. Clinical trials reported in this Focus show the drug provides analgesia simliar to that achieved with acetaminophen/codeine and aspirin/codeine combinations. Adverse effects associated with its use predominantly involve the central nervous system and the gastrointestinal tract. Tramadol's dual mechanism of action, its low respiratory depressant effect, and low abuse potential make it a unique drug within the classes of analgesic agents currently avaliable in the United States and an agent to consider for formulary inclusion.

L11 ANSWER 76 OF 78 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 94129329 EMBASE
DN 1994129329
TI [Antidepressant drugs and chronic pain].
LES ANTIDEPRESSEURS DANS LES DOULEURS CHRONIQUES.
AU Desmeules J.; Allaz A.-F.; Piguet V.; Celik Y.; Steiner N.; Dayer P.
CS Division de Pharmacologie, Hopital Cantonal Universitaire,1211 Geneve 14, Switzerland
SO Medecine et Hygiene, (1994) 52/2022 (863-869).
ISSN: 0025-6749 CODEN: MEHGAB
CY Switzerland
DT Journal; General Review
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA French
SL French; English
AB Increasing evidence exists to suggest that antidepressant drugs present an intrinsic analgesic effect which is independent of their action on mood and sedation. However, the antidepressant's lack of receptor selectivity and the number of their active metabolites, as well as the down regulation of receptors after chronic administration makes it difficult to establish their precise mechanism of action. Nevertheless, controlled studies have distinguished selected drugs that offer an **analgesic** activity. Thus, in neuropathic **pain**, the mixed tricyclic antidepressant drugs appear to be more efficient than those which selectively **inhibit** the **uptake** of serotonin or **noradrenaline**. In a small range of other **painful** conditions (headache and some rheumatologic diseases) antidepressant drugs can also be beneficial.

L11 ANSWER 77 OF 78 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 90177634 EMBASE
DN 1990177634
TI Painful peripheral neuropathies: Mechanisms and treatment.
AU Dubner R.; Max M.B.
CS Neurobiology and Anesthesiology Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892, United States
SO Serotonin and pain: proceedings of the International Symposium on Serotonin and pain. ICS879, (1990) (327-338+336).
Conference: The International Symposium on Serotonin and pain, La Roque-Gageac, FRANCE, 17 SEP 1989 - 21 SEP 1989 Editor: Besson J.-M.
Publisher: Elsevier Science Publishers B.V.

ISBN: 044481115X
DT Conference; Conference Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English

AB Painful peripheral neuropathies are among the most difficult chronic pain problems to treat. Recent studies in the peripheral and central nervous system indicate that there are multiple underlying mechanisms of neuropathic pain. A number of pathological changes take place in the peripheral nervous system following nerve injury and appear to be important for the painful conditions to occur. When a nerve is damaged, axons sprout from the site of injury and form a neuroma. The new nerve sprout amit spontaneous discharges and are responsive to mechanical, thermal and chemical stimulation. Ectopic discharges can also arise from the cell body of primary afferent neurons with consequences similar to spontaneous activity arising from neuromas. Another mechanism of pathological transmission in damaged nerve is cross-excitation from one nerve fiber to another. Such a mechanism can lead to activation of damaged nociceptive fibers via cross-excitation with intact mechanoreceptive afferents. Following peripheral nerve injury, there also is an alteration in the receptive field organization of nociceptive neurons in the medullary and spinal dorsal horns. Paripheral deafferentation leads to an expansion of the receptive fields of these neurons that is likely related to a loss of inhibitory mechanisms in the dorsal horn. The expanded receptive fields will lead to a greater number of nociceptive neurons activated by the stimulus which may ultimately be perceived as more intense pain. Thus, we can postulate that peripheral nerve injury results in ectopic discharges which ultimately results in a loss of central inhibition, expanded eceptive fields of central nociceptive neurons, hyperexcitability and increased perceived pain. The pathophysiology involves alterations in both peripheral and central nervous system mechanisms related to the processing of nociceptive information. Therapies that reverse this loss of central inhibition are effective analgesic agents in the treatment of painful neuropathies. This includes anticonvulsive agents such as carbamazepine and phenytoin. Recent studies have shown that tricyclic antidepressants are effective analgesic agents for **painful** neuropathies. Their efficacy is independent of the drugs' effects on mood. Their mechanism of action is linked to the **blockage** of the synaptic **reuptake** of serotonin or **norepinephrine**, putative inhibitory chemical mediators in the dorsal horn. All effective tricyclic antidepressants evaluated under control conditions **block norepinephrine reuptake** or have active metabolites that do so. The findings suggest that serotoninergic mechanisms may not be essential for the **analgesic** effects of tricyclic antidepressants.

L11 ANSWER 78 OF 78 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 74186118 EMBASE
DN 1974186118
TI In vitro inhibitory effects of narcotic analgesics and other psychotropic drugs on the active uptake of norepinephrine in mouse brain tissue.
AU Carmichael F.J.; Israel Y.
CS Dept. Pharmacol., Univ. Toronto, Canada
SO Journal of Pharmacology and Experimental Therapeutics, (1973) 186/2 (253-260).
CODEN: JPETAB
DT Journal
FS 037 Drug Literature Index
030 Pharmacology

[redacted]

024 Anesthesiology

LA English

AB The effect of several narcotic analgesics and other psychotropic compounds on the uptake of 3H norepinephrine by mouse brain slices or synaptosomes was studied. Codeine, hydromorphone, levorphanol, pethidine, methadone, morphine and naloxone **inhibited** the **uptake** of **norepinephrine**. However, there was no correlation between their inhibitory potency and their **analgesic** potency. Naloxone failed to antagonize the inhibitory effect of morphine. No difference in inhibitory potency of the (+) and (-) isomers of methadone on the uptake of norepinephrine was found. Chronic administration of morphine in a schedule which rendered the animals physically dependent on morphine had no effect on the uptake of norepinephrine by brain slices or synaptosomes. The above findings suggest that an inhibition of the uptake of norepinephrine is not involved in the in vivo effects of morphine. Several other psychotropic drugs such as desipramine, chlorpromazine and benzatropine were found to be potent inhibitors of the uptake of norepinephrine in vitro. A highly significant correlation was observed between the inhibition of uptake of norepinephrine by all the compounds studied and their lipid solubility, expressed as octanol/water partition coefficients. The minimal inhibitory potency of other psychotropic compounds on the active uptake of norepinephrine can be predicted from their lipid solubility.

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FILE 'HOME' ENTERED AT 08:17:58 ON 08 OCT 2001

=> d his

     (FILE 'HOME' ENTERED AT 08:17:58 ON 08 OCT 2001)

=> s reboxetine(3a)(s,s or (s,s))
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.60       0.60

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=> s reboxetine(3a)(s,s or (s,s))
L1          31 REBOXETINE(3A)(S,S OR (S,S))

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2          10 DUP REM L1 (21 DUPLICATES REMOVED)

=> d 1-10 bib,ab

L2   ANSWER 1 OF 10  CA  COPYRIGHT 2001 ACS
AN   134:105849  CA
TI   Highly selective norepinephrine reuptake inhibitors and methods of using
     the same
IN   Wong, Erik H. F.; Ahmed, Saeeduddin; Marshall, Robert Clyde; McArthur,
     Robert; Taylor, Duncan P.; Birgerson, Lars; Cetera, Pasquale
PA   Pharmacia & Upjohn Company, USA
SO   PCT Int. Appl., 48 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2001001973      A2   20010111       WO 2000-US17256  20000622
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-141968 P 19990701
US 1999-144131 P 19990716
US 1999-158256 P 19991006
US 1999-170381 P 19991213

AB Methods and compns. for treating humans suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or a condition where inhibiting reuptake of norepinephrine is a benefit are disclosed. The compns. comprise a compd. having a high pharmacol. selectivity with respect to norepinephrine reuptake sites compared to serotonin reuptake sites. The pharmacol. selectivity of serotonin (Ki)/norepinephrine (Ki) is at least about 5000, preferably about 10,000-12,000. Examples of such compds. include reboxetine in an amt. of 6-10 mg/day, and more preferably optically pure (S,S) enantiomer substantially free of (R,R) reboxetine. The methods generally include administration of a therapeutic amt. of such compns. Prepn. of a medicament from the compn., and uses of the compn. in a manuf. of the medicament to treat a human suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or condition are also disclosed. For example, **(S,S)-reboxetine** was about 5-8 fold more potent than racemic reboxetine in respect to inhibiting the reuptake of norepinephrine in rats. The selectivity of Ki of serotonin/norepinephrine for **(S,S)-reboxetine** and racemic **reboxetine** was 12,770 and 81, resp.

L2 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
AN 2001510027 IN-PROCESS
DN 21441551 PubMed ID: 11557914
TI Lack of effect of reboxetine on cardiac repolarization.
AU Fleishaker J C; Francom S F; Herman B D; Knuth D W; Azie N E
CS Clinical Pharmacology Unit, Pharmacia & Upjohn, Inc.
SO CLINICAL PHARMACOLOGY AND THERAPEUTICS, (2001 Sep) 70 (3) 261-9.
Journal code: DHR; 0372741. ISSN: 0009-9236.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ED Entered STN: 20010917
Last Updated on STN: 20010917

AB OBJECTIVE: The effect of reboxetine on electrocardiographic parameters, particularly the QTc interval, was assessed in 20 healthy subjects (15 male, 5 female). METHODS: In a 5-way crossover study, subjects received placebo, 2 mg, 4 mg, or 6 mg reboxetine, or 6 mg reboxetine and 200 mg ketoconazole twice daily for 7 days. Plasma samples, vital signs, and 12-lead electrocardiograms (ECGs) were obtained during one dosing interval of days 1, 4, and 7. Additional ECGs were recorded immediately after an exercise paradigm, so that the RR versus QT relationship might be used in calculating QTc. Plasma concentrations of R,R (-)reboxetine and the more active **S,S** (+)**reboxetine** were measured by HPLC-dual mass spectrometry. RESULTS: No statistically significant differences among treatments in mean dose-corrected pharmacokinetic parameters were observed, except that the dose-corrected area under the

concentration-time curve from time zero to 12 hours and the peak plasma concentration were significantly increased on days 4 and 7 in the presence of ketoconazole. As expected, heart rate increased from baseline (approximately 8-11 beats/min) at >/=8 mg reboxetine daily. No statistically significant prolongation of QTc (Fridericia correction) occurred after any of the treatments. No relationships between DeltaQTc and plasma concentrations of reboxetine enantiomers were apparent. Similar results were obtained with Bazett's correction and two linear corrections that relied on exercise data generated before drug administration. CONCLUSIONS: Reboxetine, at systemic exposures approximately twice the recommended dose, did not significantly affect cardiac repolarization in healthy subjects. Use of QT versus RR relationship in the drug-free state to correct QT for heart rate in the drug-treated state may provide an acceptable alternative to classic correction equations.

L2 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 2001:331091 BIOSIS
DN PREV200100331091
TI Pharmacokinetics of reboxetine in healthy volunteers with different ethnic descents.
AU Hendershot, Pamela E.; Fleishaker, Joseph C. (1); Lin, Keh-Ming; Nuccio, Inocencia D.; Poland, Russell E.
CS (1) Clinical Pharmacology II, Pharmacia and Upjohn, Inc., 7215-24-205, Kalamazoo, MI, 49007: joseph.c.fleishaker@am.pnu.com USA
SO Psychopharmacology, (May, 2001) Vol. 155, No. 2, pp. 148-153. print. ISSN: 0033-3158.
DT Article
LA English
SL English
AB Rationale: Ethnicity can affect the pharmacokinetics and pharmacodynamics of psychopharmacologic drugs. Objectives: Reboxetine disposition differences among Asians, blacks, and Caucasians were examined. Methods: Healthy subjects (12 Asians, 12 blacks, 12 Caucasians) received a single oral dose of one 4-mg reboxetine tablet in an open label, parallel study design. Plasma concentrations of reboxetine enantiomers (R,R(-) **reboxetine** and predominantly active **S,S**(+) **reboxetine**) were quantified using HPLC-MS-MS. Plasma unbound fractions of reboxetine enantiomers were evaluated by equilibrium dialysis. Ethnic group effects on pharmacokinetic parameters were assessed by ANOVA. Results: Mean **S,S**(+) **reboxetine** CLPO for blacks was significantly greater, compared to Asians and Caucasians (154+-82 ml/min, 101+-19 ml/min and 101+-18 ml/min, respectively). Mean **S,S**(+) **reboxetine** free fractions (fu) were significantly greater for Asians and blacks, compared to Caucasians (3.04+-1.28%, 2.89+-0.69%, and 1.99+-0.58%, respectively). **S,S**(+) **Reboxetine** unbound clearance (CLu) was significantly less for Asians, compared to blacks and Caucasians (3742+-1468 ml/min, 5187+-2027 ml/min, and 5294+-1163 ml/min, respectively). **S,S**(+) **Reboxetine** mean unbound AUC (AUCu) in these groups were 20.2+-7.1 ng.h/ml, 14.6+-5.1 ng.h/ml, and 13.2+-3.2 ng.h/ml, respectively. AUCu was significantly greater for Asians. CLu and AUCu did not differ significantly between blacks and Caucasians. Ethnic effects of R,R(-) reboxetine were similar to those observed for **S,S**(+) **reboxetine**. Conclusions: The AUCu difference between Asian and black and Caucasian subjects was modest. Tolerability differences among groups were not observed. No dosage adjustment is necessary for Asians or blacks.

L2 ANSWER 4 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 3
AN 134:80374 CA

09/599,213

TI Pharmacokinetics and metabolism of reboxetine
AU Fleishaker, Joseph C.
CS Clinical Pharmacology Unit, Pharmacia and Upjohn Inc., Kalamazoo, MI, 49007, USA
SO Rev. Contemp. Pharmacother. (2000), 11(5), 283-293
CODEN: RCPHFW; ISSN: 0954-8602
PB Marius Press
DT Journal; General Review
LA English
AB A review with few refs. Reboxetine is a novel selective noradrenaline inhibitor developed as an antidepressant. Reboxetine pharmacokinetics is linear over a single-dose range up to 5 mg, and a multiple-dose range up to 12 mg/day. The terminal elimination half-life is approx. 12 h. The recommended clin. dose is 8-10 mg/day in 2 divided doses. The abs. bioavailability of reboxetine is >94%, indicating essentially complete absorption and minimal 1st-pass metab. Reboxetine is highly bound (>98%) to plasma proteins, primarily .alpha.1-acid glycoprotein. Less than 10% of the reboxetine dose is eliminated in the urine as intact drug; the balance of the dose is eliminated through hepatic metab., predominantly via CYP3A4. Plasma concns. of reboxetine are increased in elderly subjects and in subjects with hepatic or renal dysfunction. The mechanism for these effects appears to be reduced metabolic clearance. Drug interactions do not occur between reboxetine and quinidine or fluoxetine. Ketoconazole decreases the clearance of reboxetine by approx. 30%. Reboxetine has no effect on the in vitro activity of CYP1A2, CYP2C9, CYP2D6, CYP2E1, or CYP3A4 at therapeutic concns. In vivo reboxetine has no effect on the dextromethorphan/dextrorphan ratio, a measure of CYP2D6 activity. Thus, reboxetine is not expected to affect the pharmacokinetics of other drugs metabolized by cytochrome P 450. Reboxetine is a racemic mixt.; the S,S(+) enantiomer is apparently responsible for the therapeutic and adverse effects seen after reboxetine administration. The ratio of area under the curve values for R,R(-) to **S,S**(+) **reboxetine** is approx. 2:1. Chiral inversion does not occur, and pharmacokinetic differences between enantiomers are the result of stereoselective protein binding.
RE.CNT 32
RE
(1) Avenoso, A; Ther Drug Monit 1999, V21, P577 CA
(3) Benedetti, M; Chirality 1995, V7, P285 CA
(4) Caccia, S; Drug Dispos 1998, V34, P281 CA
(5) Cocchiara, G; Eur J Drug Metab Pharmacokinet 1991, V16, P231 CA
(6) Connor, T; Eur J Pharmacol 1999, V379, P125 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 4
AN 132:30273 CA
TI Cytochrome P-450-mediated metabolism of the individual enantiomers of the antidepressant agent reboxetine in human liver microsomes
AU Wienkers, Larry C.; Allievi, Cecilia; Hauer, Michael J.; Wynalda, Michael A.
CS Department of Drug Metabolism, Pharmacia and Upjohn, Kalamazoo, MI, 49007, USA
SO Drug Metab. Dispos. (1999), 27(11), 1334-1340
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB In vitro studies were conducted to identify the hepatic cytochrome P 450 (CYP) enzymes responsible for the oxidative metab. of the individual enantiomers of reboxetine. In human liver microsomes, each reboxetine

enantiomer was metabolized to one primary metabolite, O-desethylreboxetine, and three minor metabolites, two arising via oxidn. of the ethoxy arom. ring and a third yet unidentified metabolite. Over a concn. range of 2 to 200 .mu.M, the rate O-desethylreboxetine formation for either enantiomer conformed to monophasic Michaelis-Menten kinetics. Evidence for a principal role of CYP3A in the formation of O-desethylreboxetine for (**S,S**)-**reboxetine** and (R,R)-reboxetine was based on the results from the following studies: 1) inhibition of CYP3A activity by ketoconazole markedly decreased the formation of O-desethylreboxetine, whereas inhibitors selective for other CYP enzymes did not inhibit reboxetine metab., 2) formation of O-desethylreboxetine correlated ($r^2 = 0.99$; $p < .001$) with CYP3A-selective testosterone 6-.beta.-hydroxylase activity across a population of human livers ($n = 14$). Consistent with inhibition and correlation data, O-desethylreboxetine formation was only detectable in incubations using microsomes prepd. from a Baculovirus-insect cell line expressing CYP3A4. Furthermore, the apparent KM for the O-desethylation of reboxetine in cDNA CYP3A4 microsomes was similar to the affinity consts. detd. in human liver microsomes. In addn., (**S,S**)-**reboxetine** and (R,R)-reboxetine were found to be competitive inhibitors of CYP2D6 and CYP3A4 (Ki = 2.5 and 11 .mu.M, resp.). Based on the results of the study, it is concluded that the metab. of both reboxetine enantiomers in humans is principally mediated via CYP3A.

RE.CNT 32

RE

(1) Bertz, R; Clin Pharmacokinet 1997, V32, P210 CA
(2) Caldwell, J; J Chromatogr A 1995, V694, P39 CA
(3) Cheng, Y; Biochem Pharmacol 1973, V22, P3099 CA
(4) Cocchiara, G; Eur J Drug Metab Pharmacokinet 1991, V16, P231 CA
(5) Desta, Z; J Pharmacol Exp Ther 1998, V285, P428 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 5

AN 132:202649 CA

TI Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans

AU Herman, Beth D.; Fleishaker, Joseph C.; Brown, Mark T.

CS Clinical Pharmacology and CNS Clinical Development Units, Pharmacia and Upjohn, Inc., Kalamazoo, MI, 49007, USA

SO Clin. Pharmacol. Ther. (St. Louis) (1999), 66(4), 374-379
CODEN: CLPTAT; ISSN: 0009-9236

PB Mosby, Inc.

DT Journal

LA English

AB Ketoconazole is a potent inhibitor of the cytochrome P 450 3A4 enzyme. Reboxetine, a selective norepinephrine reuptake inhibitor, is metabolized by cytochrome P 450 3A4. The potential interaction of reboxetine with this representative from the azole deriv. class was examd. Healthy volunteers received: (1) 4 mg reboxetine orally on the 2nd day of a 5-day regimen of 200 mg ketoconazole once daily; and (2) 4 mg reboxetine orally in a crossover design. Plasma concns. of reboxetine enantiomers [(R,R)-(-)-reboxetine and the more active (**S,S**)-(+)-**reboxetine**] were measured by HPLC-tandem mass spectrometry. Ketoconazole increased (R,R)-(-)-**reboxetine** and (**S,S**)-(+)-**reboxetine** mean area under the plasma concn.-time curves (AUC) by 58% and 43%, resp. Oral clearance of both enantiomers was consequently decreased 34% and 24%, resp., by ketoconazole. Ketoconazole did not significantly affect maximal plasma concns. Mean terminal half-lives of the enantiomers after administration of ketoconazole (21.5 h and 18.9 h, resp.) were longer than after reboxetine alone (14.8 h and

14.4 h, resp.). The AUC ratio of (R,R)-(-)-**reboxetine** to (**S,S**)-(+)-**reboxetine** was reduced by ketoconazole administration. Thus, ketoconazole decreases the clearance of both reboxetine enantiomers. Although the adverse effect profile for reboxetine was not altered by ketoconazole, the results of this study suggest that caution should be used and that a redn. in reboxetine dose should be considered when the two are coadministered.

RE.CNT 18
RE
(2) Bedford, T; Drug Saf 1996, V15, P167 CA
(4) Cocchiara, G; Eur J Drug Metab Pharmacokinet 1991, V16, P231 CA
(5) Edwards, D; Biopharm Drug Dispos 1995, V16, P443 CA
(6) Fleishaker, J; Biopharm Drug Dispos 1999, V20, P53 CA
(9) Jones, T; Clin Pharmacokinet 1997, V32, P357 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 6
AN 132:30638 CA
TI Hemodynamic effects of reboxetine in healthy male volunteers
AU Denolle, Thierry; Pellizzoni, Cinzia; Jannuzzo, M. Gabriella; Poggesi, Italo
CS Biotrial Research Centre, Rennes, 35000, Fr.
SO Clin. Pharmacol. Ther. (St. Louis) (1999), 66(3), 282-287
CODEN: CLPTAT; ISSN: 0009-9236
PB Mosby, Inc.
DT Journal
LA English
AB Background: Reboxetine [(R,S)-2[(R,S)-.alpha.-(2-ethoxyphenoxy)benzyl]morpholine methanesulfonate] is a racemic compd. that consists of equal proportions of R,R- and S,S-enantiomers. This study investigated the hemodynamic effects of reboxetine and the R,R-enantiomer compared with placebo in volunteers. The pharmacokinetics of reboxetine and its enantiomers were also investigated in the study. Methods: Nine healthy, male volunteers received single doses of 4 mg reboxetine, 2 mg R,R-enantiomer, and placebo at weekly intervals. Reboxetine and the R,R-enantiomer were well tolerated in all volunteers. Results: The heart rates of patients in the supine and standing positions were increased after reboxetine administration compared with the R,R-enantiomer ($P < .05$, except supine heart rate at 6 h) and placebo ($P < .05$). Supine systolic and diastolic blood pressure was also increased by 3 .+-. 4 and 1 .+-. 4 mm Hg, resp., after reboxetine compared with the R,R-enantiomer (-2 .+-. 4 and -4 .+-. 3 mm Hg) and placebo (-4 .+-. 4 and -4 .+-. 4 mm Hg) administration. The systolic and diastolic blood pressure measurements for subjects while standing did not differ significantly among treatments. There was no significant difference between the max. plasma concn., mean time to max. plasma concn., plasma half-life, or area under the plasma concn.-time curve (AUC) of the R,R-enantiomer after reboxetine or R,R-enantiomer administration. The ratio of the mean AUC values for the R,R- and S,S-enantiomers was 2.1. Conclusion: These findings suggest that the S,S-enantiomer is responsible for the hemodynamic effects of reboxetine in humans. Increases in supine blood pressure after reboxetine administration may be interpreted as regression to the mean value and not caused by any treatment effect.

RE.CNT 19
RE
(2) Edwards, D; Biopharm Drug Dispos 1995, V16, P443 CA
(3) Frigerio, E; Chirality 1997, V9, P303 CA
(5) Hamilton, M; Br J Clin Pharmacol 1983, V15, P367 CA
(6) Melloni, P; Eur J Med Chem Clin Ther 1984, V19, P235 CA
(7) Melloni, P; Tetrahedron 1985, V41, P1393 CA

09/599,213

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 7
AN 132:102425 CA
TI Evaluation of the potential pharmacokinetic/pharmacodynamic interaction between fluoxetine and reboxetine in healthy volunteers
AU Fleishaker, Joseph C.; Herman, Beth D.; Pearson, Laura K.; Ionita, Antoaneta; Mucci, Massimiliano
CS Clinical Pharmacology II, Pharmacia & Upjohn, Inc., Kalamazoo, MI, USA
SO Clin. Drug Invest. (1999), 18(2), 141-150
CODEN: CDINFR; ISSN: 1173-2563
PB Adis International Ltd.
DT Journal
LA English
AB Objective: This study was performed to assess the tolerability of combined administration of reboxetine, a selective noradrenaline (norepinephrine) reuptake inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor, relative to administration of each drug sep. Design: The following treatments were administered for 8 days according to a randomized, double-blind, placebo-controlled parallel design: (a) oral reboxetine 4 mg twice daily, (b) oral fluoxetine 20 mg once daily, or (c) oral reboxetine 4 mg twice daily and fluoxetine 20 mg once daily. Participants: Thirty healthy, nonsmoking volunteers (27 male, three female), aged between 20 and 55 yr and within 15% of normal bodyweight were included in the study. Target Parameters: Plasma reboxetine enantiomers were quantified using HPLC-MS-MS. Fluoxetine and norfluoxetine concns. were detd. using high performance liq. chromatog. Pharmacokinetic parameters were compared by unpaired t-test. Clin. lab. data were analyzed as the change from baseline, and adverse events were tabulated by treatment. Vital sign and Digit Symbol Substitution Test (DSST) data were analyzed by repeated measures anal. of variance. Results: The adverse event profiles were similar for combined reboxetine and fluoxetine relative to administration of each drug sep. Reboxetine significantly increased mean standing and supine heart rate vs. baseline, whereas heart rate was not modified by fluoxetine. No significant treatment effects were seen for DSST scores or oral temp. The area under the plasma concn.-time curve from 0 to 12 h for **S,S**(+) **reboxetine** was approx. 23% higher with fluoxetine coadministration than with reboxetine alone, but this effect, as well as effects on other pharmacokinetic parameters for either reboxetine enantiomer, was not statistically significant. In addn., no significant effects of reboxetine on fluoxetine or norfluoxetine pharmacokinetics were obsd. Conclusion: Combined administration of reboxetine and fluoxetine was well tolerated in healthy volunteers. These results suggest minimal clin. impact when these drugs are administered concomitantly to depressed patients.
RE.CNT 25
RE
(2) Bergstrom, R; Clin Pharmacol Ther 1997, V62, P643 CA
(3) Cocchiara, G; Eur J Drug Metab Pharmacokinet 1991, V16, P231 CA
(4) Edwards, D; Biopharm Drug Disp 1995, V16, P443 CA
(8) Greenblatt, D; Clin Pharmacol Ther 1992, V52, P479 CA
(9) Hamelin, B; Clin Pharmacol Ther 1996, V60(5), P512 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 8
AN 130:346803 CA
TI Absolute bioavailability of reboxetine enantiomers and effect of gender on pharmacokinetics
AU Fleishaker, Joseph C.; Mucci, Massimiliano; Pellizzoni, Cinzia; Poggesi, Italo

09/599,213

CS Clinical Pharmacokinetics Unit, Pharmacia and Upjohn, Inc., Kalamazoo, MI, USA
SO Biopharm. Drug Dispos. (1999), 20(1), 53-57
CODEN: BDDID8; ISSN: 0142-2782
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB The abs. bioavailability of reboxetine enantiomers was assessed in six male and six female volunteers. In a two-way crossover study, subjects received 1.0 mg reboxetine orally and 0.3 mg reboxetine as an i.v. bolus. The R,R(-) and S,S(+) enantiomers in serial plasma and urine samples were detd. by a validated LC-MS-MS method. There were no significant differences between treatments for clearance or dose-cor. AUC0-.infin. values. The abs. bioavailability was 0.919 and 1.02 for R,R(-) **reboxetine** and **S,S**(+) **reboxetine**, resp. A secondary objective of the study was to assess gender effects on pharmacokinetics of the enantiomers. Significant differences in vol. of distribution between genders were obsd., but differences in wt.-cor. vols. were not significant. Wt.-cor. systemic clearance and oral clearance tended to be lower in males, but this difference reached statistical significance only for wt.-cor. oral clearance of R,R(-) reboxetine. Cmax after oral administration was 40 and 48% higher in women than men for R,R(-) **reboxetine** and **S,S**(+) **reboxetine**, resp. These results indicate that reboxetine enantiomers are well absorbed after oral administration and that little first-pass metab. occurs. There are no clin. significant effects of gender on the pharmacokinetics of reboxetine enantiomers.
RE.CNT 13
RE
(2) Cocchiara, G; Eur J Drug Metab Pharmacokin 1991, V16, P231 CA
(4) Edwards, D; Biopharm Drug Dispos 1995, V16, P443 CA
(6) Melloni, P; Eur J Med Chem Chim Ther 1984, V19, P235 CA
(7) Montgomery, S; J Psychopharmacol Oxf 1997, V11(4 Suppl), PS9 MEDLINE
(9) Pellizzoni, C; Biopharm Drug Dispos 1996, V17, P623 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 10 CA COPYRIGHT 2001 ACS DUPLICATE 9
AN 130:204630 CA
TI Improved enantioselective method for the determination of the enantiomers of reboxetine in plasma by solid-phase extraction, chiral derivatization, and column-switching high-performance liquid chromatography with fluorescence detection
AU Walters, Rodney R.; Buist, Susan C.
CS Pharmacokinetics and Bioanalytical Research, Pharmacia and Upjohn, Kalamazoo, MI, 49001, USA
SO J. Chromatogr., A (1998), 828(1 + 2), 167-176
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier Science B.V.
DT Journal
LA English
AB A rapid enantioselective method is described for the quantitation of the **reboxetine** (R,R)- and (**S,S**)-enantiomers in plasma utilizing solid-phase extn., derivatization, normal-phase high-performance liq. chromatog., and fluorescence detection. Plasma samples (0.1 mL) with added internal std. were applied to activated solid-phase extn. disks contg. a nonpolar/strong cation mixed-phase, washed, eluted, evapd. to dryness, and derivatized for 5 min with (+)-1-(9-fluorenyl)ethyl chloroformate. After termination of the derivatization reaction, the samples were analyzed by isocratic normal-phase HPLC using a silica column and ethanol-heptane (1:124,

vol./vol.) as mobile phase. The derivatized reboxetine peak was column-switched onto cyano and Chiralcel OD-H columns in series using ethanol-heptane (1:49, vol./vol.) as mobile phase to resolve the diastereomeric derivs. of the enantiomers and sep. interferences. The column effluent was monitored with fluorescence detection at 260/315 nm. The range of quantitation of each enantiomer was 2-2000 ng/mL. One sample was injected every 18 min.

RE.CNT 7
RE
(1) Bergqvist, Y; J Chromatogr B 1994, V652, P73 CA
(3) Einarsson, S; Anal Chem 1987, V59, P1191 CA
(4) Frigerio, E; Chirality 1997, V9, P303 CA
(5) Frigerio, E; J Chromatogr A 1994, V660, P351 CA
(6) Rosseel, M; J Chromatogr 1991, V568, P239 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 08:17:58 ON 08 OCT 2001)

FILE 'CA, BIOSIS, MEDLINE, DRUGU, EMBASE' ENTERED AT 08:19:59 ON 08 OCT 2001
L1 31 S REBOXETINE(3A)(S,S OR (S,S))
L2 10 DUP REM L1 (21 DUPLICATES REMOVED)

=> s (+)reboxetine or (+)-reboxetine
MISSING OPERATOR +)REBOXETINE
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (+)reboxetine or (+)-reboxetine
MISSING OPERATOR +)REBOXETINE
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (+)reboxetine or (+)-reboxetine
MISSING OPERATOR +)REBOXETINE
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (+)-reboxetine
MISSING OPERATOR +)-REBOXETINE
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s +reboxetine or +-reboxetine or + reboxetine
'+REBOXETINE' NOT VALID HERE
'+REBOXETINE' NOT VALID HERE
'+REBOXETINE' NOT VALID HERE
'+REBOXETINE' NOT VALID HERE
'+REBOXETINE' NOT VALID HERE

=> s "(+)reboxetine" or "(+)-reboxetine"
L3 888 "(+)REBOXETINE" OR "(+)-REBOXETINE"

=> pain? or analge?
PAIN? IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter

"HELP COMMANDS" at an arrow prompt (=>).

```
=> s pain? or analge?
L4      877609 PAIN? OR ANALGE?

=> s l3 and l4
L5          15 L3 AND L4

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           14 DUP REM L5 (1 DUPLICATE REMOVED)

=> d 1-14 bib,ab
```

L6 ANSWER 1 OF 14 CA COPYRIGHT 2001 ACS
AN 134:285613 CA
TI Treatment of fatigue, head injury and stroke with a selective noradrenaline reuptake inhibitor combined with phenylalanine or tyrosine
IN Horrobin, David F.; Loder, Cari
PA Laxdale Limited, UK
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026623	A2	20010419	WO 2000-GB3926	20001012
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	GB 2355191	A1	20010418	GB 1999-24172	19991012
PRAI	GB 1999-24172	A	19991012		

AB A method of treatment of disorders of neurol. origin and drug formulations for use in the method are disclosed. These conditions comprise fatigue and assocd. syndromes of **pain**, weakness and depressed mood which are assocd. with chronic fatigue syndrome, brain injury and stroke, stress, fibromyalgia, and irritable bowel syndrome. The treatment comprises administering to a patient in need thereof a selective inhibitor of noradrenaline reuptake combined with either phenylalanine or tyrosine in the same dosage form or the same pack. The noradrenergic drug may be selected from lofepramine, desipramine or **reboxetine**. The selective inhibitor may be a combined inhibitor of both noradrenaline and serotonin reuptake such as venlafaxine, duloxetine or milnacipran, or an inhibitor of both noradrenaline and dopamine reuptake such as bupropion.

L6 ANSWER 2 OF 14 CA COPYRIGHT 2001 ACS
AN 134:173051 CA
TI Methods and compositions for treating or preventing sleep disturbances using very low doses of cyclobenzaprine
IN Iglehart, Iredell W., III
PA Vela Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2

[redacted]

09/599,213

DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001012175	A1	20010222	WO 2000-US22082	20000811

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-148881 P 19990813

AB Methods and compns. comprising a very low dose of cyclobenzaprine or metabolite thereof are provided for preventing and treating sleep disturbances and illnesses manifested with sleep dysfunction, including fibromyalgia syndrome, chronic fatigue syndrome, sleep disorders, psychogenic **pain** disorders or chronic **pain** syndromes or symptoms thereof. Also provided are methods and compns. for treating sleep disturbances, chronic **pain** or fatigue in humans suffering from fibromyalgia syndrome, chronic fatigue syndrome, sleep disorders, psychogenic **pain** disorders, chronic **pain** syndromes using a very low dose of cyclobenzaprine.

RE.CNT 4
RE
(1) Gregorie, T; US 1339636 A 1920
(2) Khouzam; CONSULTANT 2000, V40(8), P1441
(3) Merck & Co Inc; FR 2121529 A 1972 CA
(4) Santandrea, S; JOURNAL OF INTERNATIONAL MEDICAL RESEARCH 1993, V21(2), P74 MEDLINE

L6 ANSWER 3 OF 14 CA COPYRIGHT 2001 ACS
AN 134:105849 CA
TI Highly selective norepinephrine reuptake inhibitors and methods of using the same
IN Wong, Erik H. F.; Ahmed, Saeeduddin; Marshall, Robert Clyde; McArthur, Robert; Taylor, Duncan P.; Birgerson, Lars; Cetera, Pasquale
PA Pharmacia & Upjohn Company, USA
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001001973	A2	20010111	WO 2000-US17256	20000622

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-141968 P 19990701
US 1999-144131 P 19990716

[redacted]

US 1999-158256 P 19991006
US 1999-170381 P 19991213

AB Methods and compns. for treating humans suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or a condition where inhibiting reuptake of norepinephrine is a benefit are disclosed. The compns. comprise a compd. having a high pharmacol. selectivity with respect to norepinephrine reuptake sites compared to serotonin reuptake sites. The pharmacol. selectivity of serotonin (Ki)/norepinephrine (Ki) is at least about 5000, preferably about 10,000-12,000. Examples of such compds. include **reboxetine** in an amt. of 6-10 mg/day, and more preferably optically pure (S,S) enantiomer substantially free of (R,R) **reboxetine**. The methods generally include administration of a therapeutic amt. of such compns. Prepn. of a medicament from the compn., and uses of the compn. in a manuf. of the medicament to treat a human suffering from, or preventing a human from suffering, a physiol. or psychiatric disease, disorder, or condition are also disclosed. For example, (S,S)-**reboxetine** was about 5-8 fold more potent than racemic **reboxetine** in respect to inhibiting the reuptake of norepinephrine in rats. The selectivity of Ki of serotonin/norepinephrine for (S,S)-**reboxetine** and racemic **reboxetine** was 12,770 and 81, resp.

L6 ANSWER 4 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001160947 EMBASE
TI Neurokinin(1) receptor antagonists as potential antidepressants.
AU Stout S.C.; Owens M.J.; Nemeroff C.B.
CS S.C. Stout, Lab. of Neuropsychopharmacology, Emory University School of Medicine, Department of Psychiatry, Atlanta, GA 30322, United States. sstout@learnlink.emory.edu
SO Annual Review of Pharmacology and Toxicology, (2001) 41/- (877-906). Refs: 176
ISSN: 0362-1642 CODEN: ARPTDI
CY United States
DT Journal; General Review
FS 030 Pharmacology
032 Psychiatry
037 Drug Literature Index
LA English
SL English
AB Selective, nonpeptide antagonists for tachykinin receptors first became available ten years ago. Of the three known tachykinin receptors, drug development has focused most intensively on the substance P-preferring receptor, neurokinin(1) (NK(1)). Although originally studied as potential **analgesic** compounds, recent evidence suggests that NK(1) receptor antagonists may possess antidepressant and anxiolytic properties. If confirmed by further controlled clinical studies, this will represent a mechanism of action distinct from all existing antidepressant agents. As reviewed in this chapter, the existing preclinical and clinical literature is suggestive of, but not conclusive, concerning a role of substance P and NK(1) receptors in the pathophysiology of depression and/or anxiety disorders. The ongoing clinical trials with NK(1) receptor antagonists have served as an impetus for much needed, basic research in this field.

L6 ANSWER 5 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001163654 EMBASE
TI Depression and dysthymia.
AU Moore J.D.; Bona J.R.
CS Dr. J.D. Moore, 1365 Clifton Road Northeast, Atlanta, GA 30322, United States
SO Medical Clinics of North America, (2001) 85/3 (631-644).

Refs: 58
ISSN: 0025-7125 CODEN: MCNAA
CY United States
DT Journal; General Review
FS 006 Internal Medicine
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The advances made in the 1980s and 1990s have yielded many advances in the diagnosis and treatment of depression and dysthymia. Skill of the clinician is important in sorting out the diagnosis, taking care to consider the various medical conditions that can cause depression or disguise themselves as depression. Depressive disorders are highly treatable conditions. Clinicians must overcome the stigma associated with these disorders to alleviate the **pain** and suffering of those afflicted. The advances in treatment have been enormous and continue to grow. The keys to these treatments lie in continuing to acquire the knowledge to unlock all of the causes of depression. An appendix follows listing medications commonly used in the treatment of depression or for other conditions in patients under treatment for depression.

L6 ANSWER 6 OF 14 CA COPYRIGHT 2001 ACS DUPLICATE 1
AN 133:308182 CA
TI Loss of signaling through the G protein, Gz, results in abnormal platelet activation and altered responses to psychoactive drugs
AU Yang, Jing; Wu, Jie; Kowalska, M. Anna; Dalvi, Ashutosh; Prevost, Nicolas; O'Brien, Peter J.; Manning, David; Poncz, Mortimer; Lucki, Irwin; Blendy, Julie A.; Brass, Lawrence F.
CS Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA
SO Proc. Natl. Acad. Sci. U. S. A. (2000), 97(18), 9984-9989
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Heterotrimeric G proteins mediate the earliest step in cell responses to external events by linking cell surface receptors to intracellular signaling pathways. Gz is a member of the Gi family of G proteins that is prominently expressed in platelets and brain. Here, the authors show that deletion of the .alpha. subunit of Gz in mice: (i) impairs platelet aggregation by preventing the inhibition of cAMP formation normally seen at physiol. concns. of epinephrine, and (ii) causes the mice to be more resistant to fatal thromboembolism. Loss of Gz.alpha. also results in greatly exaggerated responses to cocaine, reduces the **analgesic** effects of morphine, and abolishes the effects of widely used anti-depressant drugs that act as catecholamine reuptake inhibitors. These changes occur despite the presence of other Gi.alpha. family members in the same cells and are not accompanied by detectable compensatory changes in the level of expression of other G protein subunits. Therefore, these results provide insights into receptor selectivity among G proteins and a model for understanding platelet function and the effects of psychoactive drugs.
RE.CNT 38
RE
(1) Aktories, K; Naunyn-Schmiedebergs Arch Pharmacol 1983, V324, P196 CA
(5) Casey, P; J Biol Chem 1990, V265, P2383 CA
(6) Chan, J; J Neurochem 1995, V65, P2682 CA
(7) DiMinno, G; J Pharmacol Exp Ther 1983, V225, P57 CA

(8) Drew, K; Psychopharmacology 1990, V101, P465 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09883 DRUGU P
TI **Analgesic** efficacy of **reboxetine**.
AU Schueler P; Schaffler K; Seibel K
CS Pharmacia+Upjohn; Human-Pharmacodynamic-Res.
LO Erlangen; Munich, Ger.
SO Nervenarzt (71, Suppl. 1, S132, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Pharmacia + Upjohn, Erlangen, Germany.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AB 5 Days of **reboxetine** displayed better **analgesic** effects than placebo in a randomized, double-blind, placebo-controlled, crossover study in 24 subjects in which algesia on normal and capsaicin-irritated skin was assessed objectively by laser-SEP in the vertex EEG and also on a subjective scale . Since **reboxetine** reduced the N1 and P2-components of the SEP, its **analgesic** action is assumed to have central and peripheral (probably spinal) components. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L6 ANSWER 8 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09892 DRUGU T
TI Activity of reboxetin, a selective noradrenaline-reuptake inhibitor, in patients with **pain**.
AU Harbich T; Baumann A; Niklewski G
LO Nurnberg, Ger.
SO Nervenarzt (71, Suppl. 1, S135, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Klinik fur Psychiatrie und Psychotherapie, Klinikum Nurnberg, Prof.-Ernst-Nathan-Str. 1, 90419, Nurnberg, Germany.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AB Treatment with **reboxetine** relieved or decreased **pain** in a study in 5 patients with chronic **pain** syndrome. 1 Patient had been unsuccessfully treated with opiates, NSAID and antidepressives before complete relief of **pain** by reboxetin. There were no cardiovascular side-effects and reboxetin was well tolerated. The mechanism of action of reboxetin is discussed. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L6 ANSWER 9 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-09885 DRUGU T
TI Efficacy of the selective NARI **reboxetine** in **pain** patients.
AU Harbich T; Baumann A; Niklewski G
LO Nuremberg, Ger.
SO Nervenarzt (71, Suppl. 1, S133, 2000)
CODEN: NERVAF ISSN: 0028-2804
AV Klinik fuer Psychiatrie und Psychotherapie, Klinikum Nuremberg, Germany.
LA German
DT Journal

FA AB; LA; CT
FS Literature
AB When **reboxetine** was given to 5 patients with peripheral neuropathy and 1 with severe spinal myelopathy, there was a decrease in **pain** scores recorded on standardized, subjective **pain** scales. In one case, the **pain** caused by a severe spinal myelopathy had not been relieved by earlier opioids, NSAIDs, antidepressants or antiepileptics, but almost complete freedom from **pain** was achieved with **reboxetine**. These results suggest that both peripheral and central mechanisms are involved in the **analgesic** action of **reboxetine** and that alpha2-adrenoceptors may play a significant role. (conference abstract: Congress of the German Society for Psychiatry, Psychotherapy and Neurology, Aachen, Germany, 2000).

L6 ANSWER 10 OF 14 MEDLINE
AN 1999129494 MEDLINE
DN 99129494 PubMed ID: 9932714
TI Activity and onset of action of **reboxetine** and effect of combination with sertraline in an animal model of depression.
AU Harkin A; Kelly J P; McNamara M; Connor T J; Dredge K; Redmond A; Leonard B E
CS Department of Pharmacology, National University of Ireland, Galway.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Jan 8) 364 (2-3) 123-32. Journal code: EN6; 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990402
Last Updated on STN: 20000303
Entered Medline: 19990324
AB The limitations of antidepressant drugs to treat depression has warranted ongoing research to identify pharmacological agents and strategies which offer a faster onset of action and greater therapeutic efficacy. Noradrenaline and serotonin are widely reported to be involved in the mechanism of action of antidepressants and the recent development of selective reuptake inhibitors of these transmitters has provided the opportunity to determine the effects of targeting these transmitter systems, alone and in combination, in an antidepressant response. The present study investigated the effects of **reboxetine**, a new antidepressant that selectively inhibits noradrenaline reuptake, sertraline, a selective serotonin reuptake inhibitor and a combination treatment composed of the two drugs in the olfactory bulbectomized (OB) rat model of depression. Sub-acute (2 days) administration of **reboxetine** (2.5, 5, and 10 mg/kg, i.p.) to sham-operated and OB rats reduced the immobility time in the forced swim test. Repeated (14 days) **reboxetine** (10 mg/kg) treatment attenuated the OB-related behavioural hyperactivity in the 'open-field' test. Examination of the onset of the antidepressant effect in the 'open-field' test demonstrated that **reboxetine** (10 mg/kg), sertraline (5 mg/kg) and the combination reduced the behavioural hyperactivity after 14 days but not before this following 3, 7 or 10 days of treatment. Reduced 5-hydroxyindoleacetic acid (5-HIAA) concentrations in amygdaloid cortex of both sham and OB rats following sertraline and combination treatments are likely to be related to acute pharmacological effects on the reuptake of 5-hydroxytryptamine (5-HT). Attenuation of the hypothermia induced by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 0.05 mg/kg s.c.) and clonidine (0.1 mg/kg s.c.) occurred in the **reboxetine** and

sertraline combination treated groups following both 7 and 14 days administration indicating changes to 5-HT1A receptor and alpha2-adrenoceptor sensitivity. The results indicate that changes to 8-OH-DPAT and clonidine-induced responses occur quicker with the combination treatment than with either **reboxetine** or sertraline treatments alone.

L6 ANSWER 11 OF 14 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-36114 DRUGU P S
TI **Reboxetine**, a selective noradrenaline reuptake inhibitor, is non-sedative and does not impair psychomotor performance in healthy subjects.
AU Herrmann W M; Fuder H
CS Univ.Berlin-Free
LO Berlin, Ger.
SO Hum.Psychopharmacol. (13, No. 6, 425-33, 1998) 2 Fig. 2 Tab. 25 Ref.
CODEN: HUPSEC ISSN: 0885-6222
AV Klinikum Westend, Spandauer Damm 130, 14050 Berlin, Germany.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB A double-blind, randomized, 4-way crossover study was performed to assess the CNS effects of **reboxetine** (RB) compared to imipramine (IM) or placebo in 18 healthy volunteers. RB unlike IM had no sedative effects of electroencephalography or on any behavioral variable indicative of a decline in vigilance. Side-effects of RB administration included asthenia, dizziness, weakness, palpitations, inner unrest, dry mouth, impaired co-ordination, poor concentration, sensation of coldness/heat, disturbed vision, tingling sensation, cardiac arrhythmia, headache, nausea/vomiting and retrosternal **pain**.

L6 ANSWER 12 OF 14 MEDLINE
AN 1999033936 MEDLINE
DN 99033936 PubMed ID: 9818627
TI The measurement of retardation in depression.
AU Dantchev N; Widlocher D J
CS Groupe Hospitalier de la Salpetriere, Paris, France.
SO JOURNAL OF CLINICAL PSYCHIATRY, (1998) 59 Suppl 14 19-25.
Journal code: HIC; 7801243. ISSN: 0160-6689.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981202
AB The description of clinical features helps to distinguish between depressive illness and nondepressive psychic **pain** and enables the clinician to decide whether prescription of an antidepressant is beneficial. Psychomotor retardation is probably a central feature of depression, and this review discusses the methods available for measuring it. The Salpetriere Retardation Rating Scale (SRRS) specifically measures psychomotor retardation; the scale and applications are described. Means of measuring motor and speech activity and an experimental approach for understanding the process underlying psychomotor retardation are reviewed. Comparison of the SRRS and other rating scale scores demonstrates that retardation is related to depression severity and therapeutic change and is a good criterion for prediction of therapeutic effect. The SRRS has

been used to show that selective antidepressants target specific clinical dimensions of depression depending on the patient subgroup treated. Measures of motor and speech activity are sensitive to therapeutic response. Choice Reaction Time and Simple Reaction Time tasks are particularly suited for examining psychomotor retardation because they test the decision process while avoiding motivation and attention interference. Psychomotor retardation is a constant and probably central feature of depression. Means available for measuring it can be used to assess the effects of antidepressants on specific clinical dimensions.

L6 ANSWER 13 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998136598 EMBASE
TI The year's new drugs.
AU Graul A.I.
SO Drug News and Perspectives, (1998) 11/1 (15-32).
ISSN: 0214-0934 CODEN: DNPEED
CY Spain
DT Journal; General Review
FS 006 Internal Medicine
037 Drug Literature Index
LA English

L6 ANSWER 14 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999012138 EMBASE
TI [New drugs in 1998].
NEUE ARZNEIMITTEL 1998.
AU Hellwig B.
SO Deutsche Apotheker Zeitung, (17 Dec 1998) 138/51-52 SUPPL. (11-27).
ISSN: 0011-9857 CODEN: DAZEA2
CY Germany
DT Journal; General Review
FS 030 Pharmacology
037 Drug Literature Index
LA German